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SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: FONDA Examiner #: 71970 Date: 1-22-03
Art Unit: 1623 Phone Number 308-1620 Serial Number: 10/019325
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CM1 8B19 CM1 8A05

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Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: _____

Inventors (please provide full names): see attached list sheet

Earliest Priority Filing Date: 6-29-00

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

Jan Delaval
Reference Librarian
Biotechnology & Chemical Library
CM1 1E07 – 703-308-4498
jan.delaval@uspto.gov

Please search medium molecular weight (6,000 - 12,000 Dalton) heparin compositions per claims 1, 2, 35-56, and 67. Please also search methods of using them to

a. treat a thrombotic condition
b. prevent thrombus formation
c. inhibit Thrombus formation
d. treat deep vein thrombosis, or
e. prevent pulmonary embolism

per claims 57-66, 68, and 69. Page 9 attached shows the pentasaccharide sequence of cl. 3, and page 2 attached gives the rationale for the MW range. Thanks. K.

****

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Clerical Prep Time: 20
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Fulltext _____
Patent Family _____
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Vendors and cost where applicable

STN ✓
Dialog _____
Questel/Orbit _____
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Other (specify) _____

PTO-1590 (8-01)

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jan.delaval@uspto.gov

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FILE 'HCAPLUS' ENTERED AT 14:08:11 ON 28 JAN 2003

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FILE LAST UPDATED: 27 Jan 2003 (20030127/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot l107

L107 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN 2002:740646 HCAPLUS
TI Pharmacokinetic and pharmacodynamic characterization of a **medium-molecular-weight heparin** in comparison with UFH and LMWH
AU Alban, Susanne; Welzel, Dieter; Hemker, H. Coenraad
CS Institute of Pharmacy, University of Regensburg, Regensburg, Germany
SO Seminars in Thrombosis and Hemostasis (2002), 28(4), 369-377
CODEN: STHMBV; ISSN: 0094-6176
PB Thieme Medical Publishers, Inc.
DT Journal
LA English
CC 1 (Pharmacology)
AB Despite the well-established medical use of **heparins**, the question arises whether the efficacy-safety ratio of the available **heparins** can still be improved. Therefore, a **medium-mol.-wt. heparin** (**MMWH**), a new **heparin** with an av. **mol. wt.** of **10.5 kDa** and a narrow **mol. wt.** range (**9.5** to **11.5 kDa**) was developed. Its in vitro activities amt. to 174.9 anti-**factor Xa** (aXa) U/mg and 170.0 **antithrombin** (aIIa) U/mg. In the presented randomized, double-blind, cross-over study in healthy volunteers, the pharmacokinetics and pharmacodynamics of **MMWH** are compared with those of an unfractionated **heparin** (UFH) and a low-**mol.-wt. heparin** (LWMH; enoxaparin). After s.c. administration of **9000** aXa-U of either **heparin** in 16 volunteers, the prolongation of the activated partial **thromboplastin** time (aPTT), the aXa activity, and the aIIa activities were detd. at 11 time points spread over 24 h after injection. The ex vivo anal. revealed striking pharmacodynamic and pharmacokinetic differences between the three **heparins**. UFH had the lowest bioavailability regarding the aPTT, aXa, and aIIa activities. Enoxaparin exhibited only low aIIa activity but the highest aXa activity. Unlike UFH and enoxaparin, **MMWH** showed a high recovery of aIIa activity, which suggests that it combines the high potency to inhibit **thrombin** that characterizes UFH with the high bioavailability of

the LMWHs. Consequently, substantially lower doses are needed to bring about effects comparable to those of UFH and LMWH.

RE.CNT 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L107 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 2001:869013 HCAPLUS

DN 136:11163

TI Modified low **molecular weight heparin** that inhibits clot associated coagulation factors

IN **Weitz, Jeffrey; Hirsh, Jack**

PA Hamilton Civic Hospitals Res Dev., Inc., Can.

SO U.S. Pat. Appl. Publ., 26 pp., Cont. of U.S. Ser. No. 445,215, abandoned.
CODEN: USXXCO

DT Patent

LA English

IC ICM A61K031-727
ICS C08B037-10

NCL 514056000

CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2001046974	A1	20011129	US 2001-874009	20010606
PRAI	US 1997-72098P	P	19970606		
	US 2000-445215	B1	20000504		

AB The present invention provides compns. and methods for the treatment of **cardiovascular** diseases. More particularly, the present invention relates to modifying **thrombus** formation by administering an agent which, inter alia, is capable of (1) inactivating fluid-phase **thrombin** and **thrombin** which is bound either to **fibrin** in a clot or to some other surface by catalyzing **antithrombin**; and (2) inhibiting **thrombin** generation by catalyzing **factor Xa** inactivation by **antithrombin** III (ATIII). The compns. and methods of the present invention are particularly useful for preventing **thrombosis** in the circuit of **cardiac** bypass app. and in patients undergoing renal dialysis, and for treating patients suffering from or at risk of suffering from **thrombus**-related **cardiovascular** conditions, such as unstable angina, acute **myocardial** infarction (**heart** attack), cerebrovascular accidents (stroke), pulmonary **embolism**, deep **vein thrombosis**, **arterial thrombosis**, etc. A well-defined **heparin** 6,025 Da **mol. wt.** compd. was sepd. from low **mol. wt. heparin** (LMWH) by HPLC. The LMWH at 0.5/0.5 mg/kg was more effective than **heparin** at a dose of 75/75 units/kg.

ST low **mol wt heparin** coagulation factor; clot inhibition **heparin** low **mol wt**

IT **Artery, disease**
(**coronary**; modified low **mol. wt. heparin** inhibition of clot assocd. coagulation factors)

IT **Cardiovascular system**
(**disease**; modified low **mol. wt. heparin** inhibition of clot assocd. coagulation factors)

IT **Anticoagulants**
Atherosclerosis
Blood coagulation
Cardiopulmonary bypass
Molecular weight distribution
(modified low **mol. wt. heparin** inhibition of clot assocd. coagulation factors)

IT **9002-04-4, Factor IIa 9002-05-5, Factor Xa**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibition; modified low **mol. wt. heparin** inhibition of clot assocd. coagulation factors)

IT **9005-49-6P, Heparin**, biological studies
RL: PAC (Pharmacological activity); PUR (Purification or recovery); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modified low **mol. wt. heparin** inhibition of clot assocd. coagulation factors)

IT **9005-49-6DP, Heparin**, derivs.
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modified low **mol. wt. heparin** inhibition of clot assocd. coagulation factors)

L107 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN 2001:378764 HCAPLUS
DN 135:116942
TI Plasma levels of total and free tissue factor pathway inhibitor (TFPI) as

individual pharmacological parameters of various **heparins**

AU Alban, Susanne; Gastpar, Robert
CS Institute of Pharmacy, University of Regensburg, Regensburg, 93040, Germany

SO Thrombosis and Haemostasis (2001), 85(5), 824-829
CODEN: THHADQ; ISSN: 0340-6245
PB F. K. Schattauer Verlagsgesellschaft mbH
DT Journal
LA English
CC 1-8 (Pharmacology)

AB The release of circulating tissue factor pathway inhibitor (TFPI) into plasma by **heparins** is thought to contribute to their overall **antithrombotic** activity. In the presented study in healthy volunteers, we measured the **heparin**-induced increase of circulating total and free TFPI antigen and the anti-**Factor Xa** (aXa)- and **antithrombin** (aIIa) activity after s.c. injection of **9000** aXa-U of four different **heparins**: unfractionated **heparin** (UFH) (13.0 **kDa**), a **medium mol. wt.** (**MW**) **heparin** with a narrow **MW** range (HF) (**10.5 kDa**), certoparin (**6.0 kDa**) and enoxaparin (4.5 **kDa**). Based on the administration of equi-active aXa doses, certoparin induced the highest increase in total TFPI detd. as AUC ($p < 0.01$). The lowest effect was obsd. for UFH ($p < 0.0001$). However, the area under the curve of released free TFPI significantly increased in the order: enoxaparin < UFH < certoparin < HF, showing **MW** dependency with the exception of UFH. Comparing the effects of equi-gravimetric **heparin** doses, the **MW** dependency becomes even more pronounced. The mismatch of UFH may be due to its poor bioavailability, which becomes obvious from its low ex vivo aXa activity. In contrast to the TFPI releasing potency, the ex vivo aXa activity continuously decreased with increasing **MW**. Although the ex vivo aHa activity of the **heparins** increased in the same order like the release of free TFPI, there was no clear correlation. This is attributed to the fact that the aHa activity of **heparin** is not only dependent on the **MW**, but, in contrast to its TFPI releasing effect, also on the percentage of material with high affinity to **AT**. In conclusion, besides the aXa- and aHa activity, the TFPI releasing effect of **heparins** is an addnl. parameter of their individual pharmacol. profile.

ST TFPI **heparin antithrombotic** activity; certoparin **antithrombotic** activity TFPI; enoxaparin **antithrombotic** activity TFPI

IT **Anticoagulants**
(plasma levels of total and free tissue factor pathway inhibitor as individual pharmacol. parameters of various **heparins**, in humans)

IT 194554-71-7, Tissue factor pathway inhibitor
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(plasma levels of total and free tissue factor pathway inhibitor as individual pharmacol. parameters of various **heparins**, in humans)

IT **9002-04-4, Thrombin 9002-05-5**, blood coagulation **factor, Xa**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(plasma levels of total and free tissue factor pathway inhibitor as individual pharmacol. parameters of various **heparins**, in humans)

IT **9005-49-6, Heparin**, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(plasma levels of total and free tissue factor pathway inhibitor as

individual pharmacol. parameters of various **heparins**, in humans)

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L107 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN 2001:31543 HCAPLUS

DN 134:105837

TI **Medium molecular-weight heparin** compositions that inhibit clot associated coagulation factors for treatment of **cardiovascular** diseases

IN **Weitz, Jeffrey I.; Hirsh, Jack**

PA Hamilton Civic Hospitals Research Development, Inc., Can.

SO PCT Int. Appl., 82 pp.
CODEN: PIXXD2

DT Patent

LA English

IC ICM C08B037-10
ICS A61K031-727

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 44

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001002443	A1	20010111	WO 2000-CA774	20000629

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ,

CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
BR 2000012202 A 20020402 BR 2000-12202 20000629
EP 1192187 A1 20020403 EP 2000-941847 20000629
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
PRAI US 1999-141865P P 19990630
US 1999-154744P P 19990917
WO 2000-CA774 W 20000629

AB The present invention relates to modifying **thrombus** formation and growth by administering a **medium mol. wt**. **heparin** (**MMWH**) compn. that, inter alia, is capable of (1) inactivating fluid-phase **thrombin** as well as **thrombin** which is bound either to **fibrin** in a clot or to some other surface by catalyzing **antithrombin**; and (2) inhibiting **thrombin** generation by catalyzing **factor Xa** inactivation by **antithrombin** III (ATIII). In addn., the present invention provides methods and compns. useful for treating **cardiovascular** disease. The **MMWH** compns. have an **antifactor IIa** activity of .apprx.40-100 U/mg and an **antifactor Xa** activity of .apprx.90-150 U/mg.

ST **medium mol wt heparin**
antithrombotic anticoagulant

IT **Cardiovascular system**
(**disease**, treatment of; **medium mol.-wt. heparin** compns. that inhibit clot assocd. coagulation factors for treatment of **cardiovascular diseases**)

IT **Anticoagulants**
(**medium mol.-wt. heparin** compns. that inhibit clot assocd. coagulation factors for treatment of **cardiovascular** diseases)

IT **9025-39-2, Heparinase**
RL: CAT (Catalyst use); USES (Uses)
(depolymn. catalyst; **medium mol.-wt. heparin** compns. that inhibit clot assocd. coagulation factors for treatment of **cardiovascular** diseases)

IT **9005-49-6P, Heparin**, biological studies
RL: IMF (Industrial manufacture); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**medium mol.-wt. heparin** compns. that inhibit clot assocd. coagulation factors for treatment of **cardiovascular** diseases)

IT 7782-77-6, Nitrous acid 7790-28-5, Sodium periodate
RL: MOA (Modifier or additive use); USES (Uses)
(oxidant; **medium mol.-wt. heparin** compns. that inhibit clot assocd. coagulation factors for treatment of **cardiovascular** diseases)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L107 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN 2000:390693 HCAPLUS
DN 133:261265
TI Inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides
AU Ahmed, Tahir; Ungo, Jaime; Zhou, Min; Campo, Carlos
CS Division of Pulmonary Disease, Mount Sinai Medical Center, University of

Miami School of Medicine, Miami Beach, FL, 33140, USA
SO Journal of Applied Physiology (2000), 88(5), 1721-1729
CODEN: JAPHEV; ISSN: 8750-7587
PB American Physiological Society
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Inhaled **heparin** has been shown to inhibit allergic bronchoconstriction in sheep that develop only acute responses to antigen (acute responders) but was ineffective in sheep that develop both acute and late airway responses (LAR) (dual responders). Because the antiallergic activity of **heparin** is **mol.-wt.** dependent, we hypothesized that **heparin**-derived oligosaccharides (<2,500) with potential anti-inflammatory activity may attenuate the LAR in the dual-responder sheep. Specific lung resistance was measured in 24 dual-responder sheep before and serially for 8 h after challenge with Ascaris suum antigen for demonstration of early airway response (EAR) and LAR, without and after treatment with inhaled **medium-**, low-, and ultralow-**mol.-wt.** (ULMW) **heparins** and "non-anticoagulant" fractions (NAF) of **heparin**. Airway responsiveness was estd. before and 24 h postantigen as the cumulative provocating dose of carbachol that increased specific lung resistance by 400%. Only ULMW **heparins** caused a dose-dependent inhibition of antigen-induced EAR and LAR and postantigen airway hyperresponsiveness (AHR), whereas low- and **medium-mol.-wt.** **heparins** were ineffective. The effects of ULMW **heparin** and ULMW NAF-**heparin** were comparable and inhibited the LAR and AHR even when administered "after" the antigen challenge. The ULMW NAF-**heparin** failed to inhibit the bronchoconstrictor response to histamine, carbachol, and leukotriene D4, excluding a direct effect on airway smooth muscle. In six sheep, segmental antigen challenge caused a marked increase in bronchoalveolar lavage histamine, which was not prevented by inhaled ULMW NAF-**heparin**. The results of this study in the dual-responder sheep demonstrate that (1) the antiallergic activity of inhaled "fractionated" **heparins** is **mol.-wt.** dependent, (2) only ULMW **heparins** inhibit the antigen-induced EAR and LAR and postantigen AHR, and (3) the antiallergic activity is mediated by nonanticoagulant fractions and resides in the ULMW chains of <2,500.
ST **heparin** oligosaccharide inhalation allergic respiratory hyperresponsiveness
IT Respiratory tract
(hyperresponsiveness; inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides)
IT Allergy inhibitors
(inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides)
IT Oligosaccharides, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides)
IT **9005-49-6, Heparin**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides)
RE.CNT 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L107 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN 1998:80660 HCAPLUS
DN 128:212878
TI Inhibition of allergic airway responses by inhaled low-**molecular -weight heparins: molecular-weight** dependence
AU Martinez-Salas, Jose; Mendelssohn, Richard; Abraham, William M.; Hsiao, Bernard; Ahmed, Tahir
CS Div. Pulmonary Diseases, Mount Sinai Mecical Center, Univ. Miami School Medicine, Miami Beach, FL, 33140, USA

SO Journal of Applied Physiology (1998), 84(1), 222-228
CODEN: JAPHEV; ISSN: 8750-7587
PB American Physiological Society
DT Journal
LA English
CC 1-7 (Pharmacology)
AB Inhaled **heparin** prevents antigen-induced bronchoconstriction and inhibits anti-IgE-mediated mast cell degranulation. We hypothesized that the antiallergic action of **heparin** may be **mol. wt.** dependent. Therefore, we studied the effects of three different low-**mol.-wt.** fractions of **heparin** [**medium-**, low-, and ultralow-**mol.-wt. heparin** (**MMWH**, LMWH, ULMWH, resp.)] on the antigen-induced acute bronchoconstrictor response (ABR) and airway hyperresponsiveness (AHR) in allergic sheep. Specific lung resistance was measured in 22 sheep before and after airway challenge with Ascaris suum antigen, without and after pretreatment with inhaled fractionated **heparins** at doses of 0.31-5.0 mg/kg. Airway responsiveness was estd. before and 2 h postantigen as the cumulative provoking dose of carbachol in breath units that increased specific lung resistance by 400%. All fractionated **heparins** caused a dose-dependent inhibition of ABR and AHR. ULMWH was the most effective fraction, with the ID causing 50% protection (ID50) against ABR of 0.5 mg/kg, whereas ID50 values of LMWH and **MMWH** were 1.25 and 1.8 mg/kg, resp. ULMWH was also the most effective fraction in attenuating AHR; the ID50 values for ULMWH, LMWH, and **MMWH** were 0.5, 2.5, and 4.7 mg/kg, resp. These data suggest that 1) fractionated low-**mol.-wt. heparins** attenuate antigen-induced ABR and AHR; 2) there is an inverse relationship between the antiallergic activity of **heparin** fractions and **mol. wt.**; and 3) ULMWH is the most effective fraction preventing allergic bronchoconstriction and airway hyperresponsiveness.
ST antiallergic **heparin mol wt** dependence; mast cell airway hyperresponsiveness antiallergic **heparin**
IT Structure-activity relationship
(allergy-inhibiting; inhibition of allergic airway responses by inhaled low-**mol.-wt. heparins: mol.-wt.** dependence)
IT Respiratory tract
(hyperresponsiveness; inhibition of allergic airway responses by inhaled low-**mol.-wt. heparins: mol.-wt.** dependence)
IT Allergy inhibitors
Antiasthmatics
Bronchodilators
Mast cell
Molecular weight
(inhibition of allergic airway responses by inhaled low-**mol.-wt. heparins: mol.-wt.** dependence)
IT **9005-49-6, Heparin**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of allergic airway responses by inhaled low-**mol.-wt. heparins: mol.-wt.** dependence)

L107 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN 1997:731475 HCAPLUS
DN 128:39544
TI **Medium-molecular-weight heparin**, and its amino acid derivatives and pharmaceutical compositions

IN Araki, Hiromasa; Nishikawa, Hiroyuki; Tanaka, Shuichi; Nakamura, Kazumoto; Otani, Hiroya; Nishimura, Yukihiro; Shimada, Chiaki; Takeda, Seiichi; Kawai, Kenzo; Kitagawa, Chizuko; Kuwahara, Masaaki; Abe, Tomoyuki
PA Fuso Pharmaceutical Industries, Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 28 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM C08B037-10
ICS A61K031-725
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 09286803	A2	19971104	JP 1997-30150	19970214
PRAI JP 1996-36693		19960223		

AB **Medium-mol.-wt. heparin** [av. **mol. wt.** 8500-9500], and its amino acid derivs. [such as heparinylarginine and heparinylglycine] and pharmaceutical compns. for use as anticoagulant, mesangial cell proliferation-inhibiting, cancer metastasis-inhibiting, complement-inhibiting, kidney disease-treating and antiallergic agents and radical scavengers are claimed. Capsules were formulated contg. heparinyl amino acid derivs. 2.5-10 and lactose 300 mg. The heparinyl amino acid derivs. showed reduced side effects and the physiol. activities were close to those of **heparin** alone.

ST **heparin** amino acid deriv pharmaceutical; anticoagulant **heparin** amino acid deriv; metastasis inhibitor **heparin** amino acid deriv; antiallergic **heparin** amino acid deriv

IT Drug delivery systems
(capsules; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Complement
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitors; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Drug delivery systems
(injections; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Allergy inhibitors
Anticoagulants
Radical scavengers
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Kidney, disease
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns. for)

IT Kidney
(mesangium, proliferation inhibitors; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Antitumor agents
(metastasis; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Amino acids, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(reaction products with **heparin**; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Drug delivery systems

(suppositories; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT Drug delivery systems
(tablets; **medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT **9005-49-6**, **Heparin**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT 56-40-6DP, Glycine, reaction product with **heparin**, biological studies 56-41-7DP, Alanine, reaction product with **heparin** 56-45-1DP, Serine, reaction product with **heparin** 56-84-8DP, Aspartic acid, reaction product with **heparin** 60-18-4DP, Tyrosine, reaction product with **heparin** 61-90-5DP, Leucine, reaction product with **heparin** 63-68-3DP, Methionine, reaction product with **heparin** 63-91-2DP, Phenylalanine, reaction product with **heparin** 71-00-1DP, Histidine, reaction product with **heparin** 74-79-3DP, Arginine, reaction product with **heparin** 147-85-3DP, Proline, reaction product with **heparin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT 2133-40-6, L-Proline methyl ester hydrochloride 2491-18-1, Methionine methyl ester hydrochloride 2491-20-5, Alanine methyl ester hydrochloride 3417-91-2, Tyrosine methyl ester hydrochloride 5680-79-5, Glycine methyl ester hydrochloride 5680-80-8, Serine methyl ester hydrochloride 7517-19-3, Leucine methyl ester hydrochloride 7524-50-7, Phenylalanine methyl ester hydrochloride 18684-16-7, Histidine methyl ester hydrochloride 22888-59-1, Arginine methyl ester hydrochloride 91588-23-7, Aspartic acid methyl ester hydrochloride
RL: RCT (Reactant); RACT (Reactant or reagent)
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

IT **9005-49-6DP**, **Heparin**, reaction products with amino acids, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**medium-mol.-wt. heparin**, and its amino acid derivs. and pharmaceutical compns.)

L107 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN **1995:935150** HCAPLUS
DN **124:45153**
TI A comparison of the activity of a **heparan** sulfate of defined **molecular weight** range (**7500**-15 000 **Da**) with **heparin** and dermatan sulfate
AU Gervasi, G. B.; Catalani, R.; Bartoli, C.; Carpita, G.; Farina, C.; Gelso, E.
CS Baldacci Research Laboratories, S.p.A., Pisa, Italy
SO Pharmacological Research (1995), 31(6), 331-6
CODEN: PHMREP; ISSN: 1043-6618
PB Academic
DT Journal
LA English
CC 1-8 (Pharmacology)
AB The fibrinolytic and anticoagulant activities of heparan sulfate (HS) and dermatan sulfate (DS) were compared with those of **heparin** using in vitro tests. The results demonstrate that HS has higher

pro-fibrinolytic activity than **heparin** and DS. Although 50 times less potent than **heparin** in inhibiting **factor IIa**, HS is three times more active than DS. The action of HS resides in HCII-mediated **factor IIa** inhibition combined with an ATIII-mediated inhibition. DS has no action on ATIII-mediated inhibition of **factor IIa**. The comparison of the anticoagulant activities of the three compds. confirmed the very limited anticoagulant effect of both HS and DS in comparison with **heparin**. The results provide insight into the mechanisms of the **antithrombotic** action of heparan sulfate and dermatan sulfate.

ST fibrinolytic anticoagulant heparan sulfate **heparin** dermatan; **antithrombotic** heparan sulfate **heparin** dermatan

IT **Anticoagulants and Antithrombotics**
Fibrinolytics
(comparison of fibrinolytic and anticoagulant activity of heparan sulfate of defined **mol. wt.** range (**7500** -15000 **Da**) with **heparin** and dermatan sulfate)

IT **9005-49-6, Heparin**, biological studies 9050-30-0, Heparan sulfate **24967-94-0**, Dermatan sulfate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparison of fibrinolytic and anticoagulant activity of heparan sulfate of defined **mol. wt.** range (**7500** -15000 **Da**) with **heparin** and dermatan sulfate)

IT **9002-04-4, Thrombin**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(comparison of fibrinolytic and anticoagulant activity of heparan sulfate of defined **mol. wt.** range (**7500** -15000 **Da**) with **heparin** and dermatan sulfate)

L107 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN **1995:672779** HCAPLUS
DN **123:101810**
TI Anticoagulant, **antithrombotic** and antihemostatic activities of **heparin**: structural requirements, mechanism of action and clinical applications
AU Nader, Helena B.; Dietrich, Carl P.
CS Dep. Bioquimica, Escola Paulista de Medicina, Sao Paulo, 04044-020, Brazil
SO Ciencia e Cultura (Sao Paulo) (1994), 46(4), 297-302
CODEN: CCUPAD; ISSN: 0009-6725
PB Sociedade Brasileira para o Progresso da Ciencia
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review, with 48 refs. The structural features for the anticoagulant, **antithrombotic** and antihemostatic activities of the **heparin mol.** as well as the resulting clin. applications are reviewed. For anticlotting activity, an intact **heparin mol.** with a min. **mol. wt.** of **8** **kDa** is necessary. For the **antithrombotic** activity, a **heparin** hexasaccharide fragment already exhibits 60% of the activity of **heparin**. Also compds. like heparan sulfate, without anticlotting activity, show the same **antithrombotic** effect of **heparin**. **Heparin**, besides its favorable anticoagulant and **antithrombotic** actions, has also a strong hemorrhagic activity. This effect is related to special structures of the damaged vessel wall and is not related to the anticoagulant and **antithrombotic** actions. The min. structure for the prodn. of hemorrhage is a disaccharide composed of glucosamine C-6 sulfate and uronic acid with an 1.fwdarw.4 glycosidic linkage. The hemorrhagic effect of **heparin** and fragments, including disaccharides, is abolished

by ATP and/or myosin. The hemorrhagic disaccharides resemble the **mol.** conformation of ATP. Topical use of ATP in patients subjected to **cardiovascular** surgery with extracorporeal circulation significantly reduced the blood loss caused by **heparin**.

ST anticoagulant **antithrombotic** antihemostatic **heparin** review

IT **Anticoagulants and Antithrombotics**
Hemorrhage
Molecular structure-biological activity relationship
(anticoagulant, **antithrombotic** and antihemostatic activities of **heparin** in relation to structural requirements, mechanism of action and clin. applications)

IT **9005-49-6, Heparin**, biological studies
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticoagulant, **antithrombotic** and antihemostatic activities of **heparin** in relation to structural requirements, mechanism of action and clin. applications)

L107 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN **1986:188565** HCAPLUS
DN **104:188565**
TI Non **thrombus**-forming **heparin**
IN Behrens, Nicolas Huberto
PA Argent.
SO Ger. Offen., 20 pp.
CODEN: GWXXBX
DT Patent
LA German
IC ICM C08B037-10
CC 44-1 (Industrial Carbohydrates)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 3531101	A1	19860313	DE 1985-3531101	19850830
	GB 2164346	A1	19860319	GB 1985-21640	19850830
	GB 2164346	B2	19880330		
PRAI	AR 1984-297810		19840831		

AB The title product was produced from normal **heparin** (I) by gel fractionation. Thus, 600 g intestinal mucosa I of bovine animal was fractionated on Biogel P 30 column using 0.5 M NaCl and d 5 mM tris-HCl as eluent to give I in 70% yield, with **mol. wt. 10,000 Dalton**, anticoagulation activity 170 USP/mg, and min. aggregation concn. .gtoreq.40 units.

ST **nonthrombus** forming **heparin** manuf

IT **9005-49-6P**, uses and miscellaneous
RL: PREP (Preparation); USES (Uses)
(**nonthrombus**-forming, manuf. of)

L107 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN **1985:464639** HCAPLUS
DN **103:64639**
TI The effect of **heparin** fragments of different **molecular weights** on experimental **thrombosis** and hemostasis
AU Bergqvist, D.; Nilsson, B.; Hedner, U.; Pedersen, P. C.; Oestergaard, P. B.
CS Malmoe Gen. Hosp., Univ. Lund, Malmoe, Swed.
SO Thrombosis Research (1985), 38(6), 589-601
CODEN: THBRAA; ISSN: 0049-3848
DT Journal

LA English
CC 1-8 (Pharmacology)
AB The effect of **heparin** [9005-49-6] fragments of different **mol. wts.** has been compared with that of conventional Na **heparin** on exptl. **thrombosis** in vivo and ex vivo and exptl. hemostasis in vivo. Fragments of different **mol. wts.** (4,900, 6,500, 9,500 and 22,200 **dalton**) including the control gave a significant prolongation of the hemostatic plug formation time in the rabbit mesenteric microcirculation, and all except the fragment with the lowest **mol. wt.** reduced the frequency of jugular **vein thrombosis** (induced by a combination of endothelial denudation and stasis). There was a correlation between the **factor Xa** [9002-05-5] inhibitory (XaI) activity of the different **heparin** fragments and frequency of **thrombosis**. A dose-dependent lag-phase until start of **thrombus** formation was found ex vivo. In a second part of the study a dose response investigation was made comparing different doses of a fragment (6500 **dalton**) with convential **heparin** in the same XaI doses (10, 30, and 60 units/kg). Na **heparin** in the highest dose prolonged the hemostatic plug formation time, whereas none of the fragment doses did. The lowest dose both of the fragment and conventional **heparin** did not reduce the frequency of **thrombosis**, whereas the two higher doses did. Thus it may be possible to obtain preventive effect on **thrombus** formation with a **heparin** fragment.
ST **heparin** fragment **thrombosis** hemostasis
IT **Blood coagulation**
Thrombosis
(inhibition of, by **heparin** fragments)
IT **9005-49-6**, biological studies
RL: BIOL (Biological study)
(fragments, hemostasis and **thrombosis** response to)
IT **9002-05-5**
RL: BIOL (Biological study)
(inhibition of, by **heparin** fragments, hemostasis and **thrombosis** inhibition in relation to)

L107 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN **1981:615258** HCAPLUS
DN **95:215258**
TI Physicochemical characterization of **heparin** fractions
AU Stone, Audrey L.
CS Lab. Neurochem., Natl. Inst. Ment. Health, Bethesda, MD, 20205, USA
SO Developments in Biochemistry (1981), 12(Chem. Biol. Heparin), 41-55
CODEN: DEBIDR; ISSN: 0165-1714
DT Journal
LA English
CC 1-13 (Pharmacodynamics)
Section cross-reference(s): 6
AB The metachromatic reactions of methylene blue:**heparin** complexes were used as a means of investigating 2 cation-binding properties of various **heparin** chains, namely, regions of ordered metachromatic binding and regions of stronger metachromatic binding. Among all samples there was no specific correlation between the stronger metachromatic binding and the biol. activity, nor was the asym. binding unique to the active chains. The degree and stability of ordered binding increased with **heparin** chain length (from 6-20 **kilodaltons** (Kd)) as did the biol. activity of the **mol. wt.** fractions. Fractions around 6 Kd or less have insufficient internal tetrasaccharides to favor the stable, ordering binding. Furthermore, the pattern seen among **mol. wt.** fractions contg. both active and inactive chains was derived from that of their active chain

components, indicating that dyes might be binding preferentially to active chains in excess **heparin**. The increase in stability of the extrinsic Cotton effect in excess anionic sites was dramatic in active chains going from 6-8 to 20 Kd. Thus, the very high specific activity of the 20 Kd active **heparin** may be related to a special structure, involving the 2 active tetrasaccharide groupings, which stabilizes ordered binding and creates the appropriate charge distribution for stronger interaction with **antithrombin**.

ST **heparin** dye binding

IT Dyes
(**heparin** binding by, metachromatic reaction of, **mol**. **size** in relation to)

IT 61-73-4D, **heparin** complexes **9005-49-6D**, methylene blue complexes
RL: RCT (Reactant); RACT (Reactant or reagent)
(metachromatic reaction of, **mol**. **size** in relation to)

L107 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN **1979:462638** HCAPLUS
DN **91:62638**
TI **Molecular weight** determination of commercial **heparin** sodium USP and its sterile solutions
AU Rodriguez, H. J.; Vanderwielen, A. J.
CS Control Anal. Res. Dev., Upjohn Co., Kalamazoo, MI, 49001, USA
SO Journal of Pharmaceutical Sciences (1979), 68(5), 588-91
CODEN: JPMSAE; ISSN: 0022-3549
DT Journal
LA English
CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 64
AB A liq. chromatog. assay for the characterization of **heparin** Na [**9041-08-1**] USP and **heparin** sterile solns. was developed. The method employs **size** exclusion chromatog. and computer-based data collection and manipulation. An examn. of com. available **heparin** showed only minor differences between the **heparins** extd. from beef lung and porcine intestinal mucosa. The **mol**. **wt**. avs. of the material and its sterile solns. were **9000-12,000 daltons**. A correlation was obsd. between av. **mol**. **wt**. and anticoagulant activity for the **heparin** sodium samples examd.

ST **heparin** sodium **mol wt**; chromatog **heparin mol wt**; anticoagulant **heparin** sodium

IT **9041-08-1**
RL: BIOL (Biological study)
(**mol**. **wt**. detn. of com.)

L107 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN **1979:179925** HCAPLUS
DN **90:179925**
TI Correlation between structure and function of **heparin**
AU Rosenberg, Robert D.; Lam, Lun
CS Sidney Farber Cancer Inst., Beth Israel Hosp., Boston, MA, USA
SO Proceedings of the National Academy of Sciences of the United States of America (1979), 76(3), 1218-22
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
CC 1-3 (Pharmacodynamics)
AB Crude porcine **heparin** [**9005-49-6**] was fractionated to obtain highly active as well as relatively inactive species of **mol**. **wt**. .apprxeq.**7000** with specific anticoagulant

activities of 360 and **12** units/mg, resp. Nitrous acid degrdn. of both of these polymers yielded a tetrasaccharide fraction, I.beta., that contained equimolar amts. of iduronic and glucuronic acids, possessed an internal N-acetylated glucosamine, and carried anhydromannitol at the reducing end position. The I.beta. tetrasaccharide derived from the highly active **heparin**, I.beta.a, was recovered in a yield of 1.1 **mol/7000 daltons**. At least 95% of the I.beta.a was a single structure that consisted of the following unique monosaccharide sequence: L-iduronic acid .fwdarw. N-acetyl-D-glucosamine-6-sulfate .fwdarw. D-glucuronic acid .fwdarw. D-glucosamine-N,6-disulfate. The I.beta. tetrasaccharide fraction from relatively inactive mucopolysaccharide, I.beta.i, was recovered in a yield of 0.3 **mol /7000 daltons** and was a mixt. of several components. Only 8.5% of the I.beta.i tetrasaccharide fraction exhibited the same uronic acid placement and sulfate group position found in I.beta.a. Thus, 2.6% of relatively inactive mucopolysaccharide **mols**. contain the unique tetrasaccharide sequence found within each **mol**. of highly active **heparin**. Given the correlation between abundance of this unique I.beta.a tetrasaccharide sequence and biol. potency, this structure represents the crit. site responsible for anticoagulant activity.

ST **heparin** mol structure activity

IT **Anticoagulants**
(**heparin**, mol. structure in relation to)

IT Molecular structure-biological activity relationship
(anticoagulant, of **heparin**)

IT **9005-49-6**, biological studies
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticoagulant activity of, mol. structure in relation to)

L107 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2003 ACS

AN **1979:165612** HCAPLUS

DN **90:165612**

TI Highly active **heparin** species with multiple binding sites for **antithrombin**

AU Rosenberg, R. D.; Jordan, R. E.; Favreau, L. V.; Lam, L. H.

CS Harvard Med. Sch., Beth Israel Hosp., Boston, MA, USA

SO Biochemical and Biophysical Research Communications (1979), 86(4), 1319-24
CODEN: BBRCA9; ISSN: 0006-291X

DT Journal

LA English

CC 13-5 (Mammalian Biochemistry)

AB Porcine **heparin** was fractionated by Sephadex G-100 gel filtration and affinity chromatog. into mucopolysaccharide species with approx. **mol. wts.** of 20,000 **daltons** and **7000 daltons**, resp. The larger component had a specific anticoagulant activity of 738 USP U-mg and contained 2 binding regions for **antithrombin**. The smaller component had a specific anticoagulant activity of 363 USP U/mg and possessed only a single interaction site for the inhibitor. This is the 1st indication that **heparin mols**. may bear multiple binding sites for **antithrombin**.

ST **antithrombin** binding site **heparin**; anticoagulant activity **heparin**

IT **Blood coagulation**
(**heparin** multiple binding sites in relation to)

IT **9005-49-6**, biological studies
RL: PRP (Properties)
(anticoagulant activity and multiple **thrombin** binding sites of)

IT **9000-94-6**
RL: BIOL (Biological study)
(**heparin** with multiple binding sites for)

L107 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN 1978:177180 HCAPLUS
DN 88:177180
TI A study of synthetic polypeptides for hemodialysis membranes
AU Klein, Elias
CS Gulf South Res. Inst., New Orleans, LA, USA
SO U. S. NTIS, PB Rep. (1977), PB-275473, 150 pp. Avail.: NTIS From: Gov. Rep. Announce. Index (U. S.) 1978, 78(6), 85
CODEN: XPBRCA; ISSN: 0099-8583
DT Report
LA English
CC 63-7 (Pharmaceuticals)
Section cross-reference(s): 34
AB Seventeen synthetic polypeptides were prepd. from a no. of poly-.alpha.-amino acids. Charged and neutral membranes and membranes contg. **heparin** [9005-49-6] binding agents were prepd. from these polymers. Membrane properties were a function of method of prepn. and amino acid compn. One polymer (poly-.gamma.-methyl-D-glutamate) (I) [25767-60-6] was carried to pilot-scale prodn. and showed an enhanced solute transport to **middle mol.-wt**. species and a controllable ultrafiltration rate. The I membrane could be rendered **antithrombogenic** by treatment with 6, 10 ionene chloride followed by heparinization. In vitro and animal studies indicate that the effect is lasting and is not a result of **heparin** leaching. In 18 mo of clin. trials, polypeptide membrane-dialyzed patients tolerated a reduced time-dialysis schedule with fewer complications than patients on equiv. reduced-time Cuprophan dialysis.
ST hemodialysis membrane polypeptide; dialysis membrane polypeptide; glutamate polymer dialysis membrane
IT Peptides, biological studies
RL: BIOL (Biological study)
(as hemodialysis membranes)
IT Dialysis
(of blood, polypeptide membranes for)
IT Membranes and Diaphragms
(dialysis, polypeptides for)
IT 25767-60-6 25868-58-0
RL: BIOL (Biological study)
(hemodialysis membrane)
IT **9005-49-6**, biological studies
RL: BIOL (Biological study)
(polypeptide membranes treated with, for hemodialysis)

L107 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2003 ACS
AN **1975:68076** HCAPLUS
DN **82:68076**
TI Relation of **molecular weight**, and sulfate content and distribution to anticoagulant activity of **heparin** preparations
AU Cifonelli, Joseph A.
CS Pritzker Sch. Med., Univ. Chicago, Chicago, IL, USA
SO Carbohydrate Research (1974), 37(1), 145-54
CODEN: CRBRAT; ISSN: 0008-6215
DT Journal
LA English
CC 1-3 (Pharmacodynamics)
AB The anticoagulant activity of fractions ranging in **mol. wt.** from 4.8 to 12.5 .times. 103 **daltons** isolated from **heparin** [9005-49-6] by-products was influenced by the sulfate content and distribution and by **mol. wt.** A **heparin** prepn. with half the 2-amino-2-deoxy-D-glucose residues substituted with N-acetyl groups retained appreciable biol. activity. The presence of multiple repeating

units contg. 2-acetamido-2-deoxy-D-glucose residues in the interior of the **mol.** decreased biol. activity.
ST **heparin** anticoagulation sulfate **mol wt**
IT Molecular structure-biological activity relationship
(blood coagulation inhibiting, of **heparin**)
IT **Blood coagulation**
(**heparin** inhibition of, **mol. wt.** and sulfate content in relation to)
IT Sulfates, biological studies
RL: BIOL (Biological study)
(of **heparin**, blood coagulation in relation to)
IT **9005-49-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(anticoagulant activity of, **mol. wt.** and sulfate content in relation to)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot l122

L122 ANSWER 1 OF 10 MEDLINE
AN 2002480826 IN-PROCESS
DN 22229830 PubMed ID: 12244484
TI Pharmacokinetic and pharmacodynamic characterization of a **medium-molecular-weight heparin** in comparison with UFH and LMWH.
AU Alban Susanne; Welzel Dieter; Hemker H Coenraad
CS Institute of Pharmacy, University of Regensburg, Germany.. Susanne.Alban@chemie.uni-regensburg.de
SO SEMINARS IN THROMBOSIS AND HEMOSTASIS, (2002 Aug) 28 (4) 369-78. Journal code: 0431155. ISSN: 0094-6176.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS IN-PROCESS; NONINDEXED; Priority Journals
ED Entered STN: 20020924
Last Updated on STN: 20021213
AB Despite the well-established medical use of **heparins**, the question arises whether the efficacy-safety ratio of the available **heparins** can still be improved. Therefore, a **medium-molecular-weight heparin** (**MMWH**), a new **heparin** with an average molecular weight of 10.5 **kDa** and a narrow molecular weight range (9.5 to 11.5 **kDa**) was developed. Its in vitro activities amount to 174.9 anti-factor Xa (aXa) U/mg and 170.0 antithrombin (aIIa) U/mg. In the presented randomized, double-blind, cross-over study in healthy volunteers, the pharmacokinetics and pharmacodynamics of **MMWH** are compared with those of an

unfractionated **heparin** (UFH) and a low-molecular-weight **heparin** (LWMH; enoxaparin). After subcutaneous administration of 9000 aXa-U of either **heparin** in 16 volunteers, the prolongation of the activated partial thromboplastin time (aPTT), the aXa activity, and the aIIa activities were determined at 11 time points spread over 24 hours after injection. The ex vivo analysis revealed striking pharmacodynamic and pharmacokinetic differences between the three **heparins**. UFH had the lowest bioavailability regarding the aPTT, aXa, and aIIa activities. Enoxaparin exhibited only low aIIa activity but the highest aXa activity. Unlike UFH and enoxaparin, **MMWH** showed a high recovery of aIIa activity, which suggests that it combines the high potency to inhibit thrombin that characterizes UFH with the high bioavailability of the LMWHs. Consequently, substantially lower doses are needed to bring about effects comparable to those of UFH and LMWH.

L122 ANSWER 2 OF 10 MEDLINE
AN 2002010419 MEDLINE
DN 21265565 PubMed ID: 11372675
TI Plasma levels of total and free tissue factor pathway inhibitor (TFPI) as individual pharmacological parameters of various **heparins**.
AU Alban S; Gastpar R
CS Institute of Pharmacy, University of Regensburg, Germany.. Susanne.Alban@chemie.uni-regensburg.de
SO THROMBOSIS AND HAEMOSTASIS, (2001 May) 85 (5) 824-9. Journal code: 7608063. ISSN: 0340-6245.
CY Germany: Germany, Federal Republic of
DT (CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL)
LA English
FS Priority Journals
EM 200202
ED Entered STN: 20020121
Last Updated on STN: 20020220
Entered Medline: 20020219
AB The release of circulating tissue factor pathway inhibitor (TFPI) into plasma by **heparins** is thought to contribute to their overall antithrombotic activity. In the presented study in healthy volunteers, we measured the **heparin**-induced increase of circulating total and free TFPI antigen and the aXa- and aIIa activity after subcutaneous (s.c.) injection of 9000 aXa-U of four different **heparins**: unfractionated **heparin** (UFH) (13.0 **kDa**), a **medium molecular weight** (MW) **heparin** with a narrow MW range (HF) (10.5 **kDa**), certoparin (6.0 **kDa**) and enoxaparin (4.5 **kDa**). Based on the administration of equi-active aXa doses, certoparin induced the highest increase in total TFPI determined as AUC ($p < 0.01$). The lowest effect was observed for UFH ($p < 0.0001$). However, the AUC of released free TFPI significantly increased in the order: enoxaparin < UFH < certoparin < HF, showing MW dependency with the exception of UFH. Comparing the effects of equi-gravimetric **heparin** doses, the MW dependency becomes even more pronounced. The mismatch of UFH may be due to its poor bioavailability, which becomes obvious from its low ex vivo aXa activity. In contrast to the TFPI releasing potency, the ex vivo aXa activity continuously decreased with increasing MW. Although the ex vivo aIIa activity of the **heparins** increased in the same order like the release of free TFPI, there was no clear correlation. This is attributed to the fact that the aIIa activity of **heparin** is not only dependent on the MW, but, in contrast to its TFPI releasing effect, also on the percentage of material with high affinity to AT. In conclusion, besides the aXa- and aIIa activity, the TFPI releasing effect of **heparins** is an additional parameter of their individual pharmacological profile.

CT Check Tags: Comparative Study; Human; Male; Support, Non-U.S. Gov't
Adolescence
Adult
Area Under Curve
Enoxaparin: AD, administration & dosage
Enoxaparin: PK, pharmacokinetics
Enoxaparin: PD, pharmacology
Factor Xa: AI, antagonists & inhibitors
Heparin: AD, administration & dosage
***Heparin: PK, pharmacokinetics**
Heparin: PD, pharmacology
Heparin, Low-Molecular-Weight: AD, administration & dosage
Heparin, Low-Molecular-Weight: PK, pharmacokinetics
Heparin, Low-Molecular-Weight: PD, pharmacology
Kinetics
***Lipoproteins: BL, blood**
Lipoproteins: DE, drug effects
Molecular Weight
Prothrombin: AI, antagonists & inhibitors
RN 9001-26-7 (Prothrombin); 9002-04-4 (Factor IIa); **9005-49-6 (Heparin)**
CN 0 (Enoxaparin); 0 (**Heparin**, Low-Molecular-Weight); 0 (Lipoproteins); 0 (certoparin); 0 (lipoprotein-associated coagulation inhibitor); EC 3.4.21.6 (Factor Xa)

L122 ANSWER 3 OF 10 MEDLINE
AN 2000259514 MEDLINE
DN 20259514 PubMed ID: 10797135
TI Inhibition of allergic late airway responses by inhaled **heparin**-derived oligosaccharides.
AU Ahmed T; Ungo J; Zhou M; Campo C
CS Division of Pulmonary Disease, University of Miami School of Medicine, Mount Sinai Medical Center, Miami Beach, Florida 33140, USA.
SO JOURNAL OF APPLIED PHYSIOLOGY, (2000 May) 88 (5) 1721-9. Journal code: 8502536. ISSN: 8750-7587.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200006
ED Entered STN: 20000706
Last Updated on STN: 20000706
Entered Medline: 20000623
AB Inhaled **heparin** has been shown to inhibit allergic bronchoconstriction in sheep that develop only acute responses to antigen (acute responders) but was ineffective in sheep that develop both acute and late airway responses (LAR) (dual responders). Because the antiallergic activity of **heparin** is molecular-weight dependent, we hypothesized that **heparin**-derived oligosaccharides (<2, 500) with potential anti-inflammatory activity may attenuate the LAR in the dual-responder sheep. Specific lung resistance was measured in 24 dual-responder sheep before and serially for 8 h after challenge with Ascaris suum antigen for demonstration of early airway response (EAR) and LAR, without and after treatment with inhaled **medium-**, low-, and ultralow-molecular-weight (ULMW) **heparins** and "non-anticoagulant" fractions (NAF) of **heparin**. Airway responsiveness was estimated before and 24 h postantigen as the cumulative provocating dose of carbachol that increased specific lung resistance by 400%. Only ULMW **heparins** caused a dose-dependent inhibition of antigen-induced EAR and LAR and postantigen airway hyperresponsiveness (AHR), whereas low- and **medium-molecular-weight heparins** were ineffective. The effects of ULMW **heparin** and ULMW NAF-**heparin** were comparable and

inhibited the LAR and AHR even when administered "after" the antigen challenge. The ULMW NAF-**heparin** failed to inhibit the bronchoconstrictor response to histamine, carbachol, and leukotriene D(4), excluding a direct effect on airway smooth muscle. In six sheep, segmental antigen challenge caused a marked increase in bronchoalveolar lavage histamine, which was not prevented by inhaled ULMW NAF-**heparin**. The results of this study in the dual-responder sheep demonstrate that 1) the antiallergic activity of inhaled "fractionated" **heparins** is molecular-weight dependent, 2) only ULMW **heparins** inhibit the antigen-induced EAR and LAR and postantigen AHR, and 3) the antiallergic activity is mediated by nonanticoagulant fractions and resides in the ULMW chains of <2,500.

CT Check Tags: Animal; Female
Administration, Inhalation
Airway Resistance: DE, drug effects
Antigens: IM, immunology
Bronchial Hyperreactivity: IM, immunology
Bronchial Hyperreactivity: PC, prevention & control
*Bronchoconstriction: DE, drug effects
Carbachol: PD, pharmacology
Cholinergic Agonists: PD, pharmacology
Dose-Response Relationship, Drug
Heparin: CH, chemistry
***Heparin: PD, pharmacology**
Histamine: PD, pharmacology
*Hypersensitivity: PP, physiopathology
Leukotriene D4: PD, pharmacology
Molecular Weight
Oligosaccharides: CH, chemistry
*Oligosaccharides: PD, pharmacology
Sheep
Time Factors

RN 51-45-6 (Histamine); 51-83-2 (Carbachol); 73836-78-9 (Leukotriene D4); **9005-49-6 (Heparin)**

CN 0 (Antigens); 0 (Cholinergic Agonists); 0 (Oligosaccharides)

L122 ANSWER 4 OF 10 MEDLINE

AN 1999130167 MEDLINE

DN 99130167 PubMed ID: 9931190

TI Molecular-weight-dependent effects of nonanticoagulant **heparins** on allergic airway responses.

AU Campo C; Molinari J F; Ungo J; Ahmed T

CS Division of Pulmonary Diseases, University of Miami School of Medicine, Mount Sinai Medical Center, Miami Beach, Florida 33140, USA.

SO JOURNAL OF APPLIED PHYSIOLOGY, (1999 Feb) 86 (2) 549-57.
Journal code: 8502536. ISSN: 8750-7587.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199903

ED Entered STN: 19990402
Last Updated on STN: 19990402
Entered Medline: 19990322

AB We have hypothesized that antiallergic activity of inhaled **heparin** is molecular weight dependent and mediated by "nonanticoagulant fractions" (NAF-**heparin**). Therefore, we studied comparative effects of high-, **medium**-, and ultralow-molecular-weight (HMW, **MMW** , and ULMW, respectively) NAF-**heparins** on acute bronchoconstrictor response (ABR) and airway hyperresponsiveness (AHR) in allergic sheep. Specific lung resistance was measured in 23 allergic sheep, before and immediately after challenge with Ascaris suum antigen, without and after pretreatment with inhaled NAF-**heparins**. Airway

responsiveness was estimated before and 2 h postantigen as the cumulative provocating dose of carbachol in breath units, which increased specific lung resistance by 400%. NAF-**heparins** attenuated ABR and AHR in a molecular-weight-dependent fashion. HMW NAF-**heparin** (n = 8) was the least effective agent: it attenuated ABR [inhibitory dose causing 50% protection (ID50) = 4 mg/kg] but had no effect on AHR. **MMW** NAF-**heparin** (n = 8) showed **intermediate** efficacy (ABR ID50 = 0.8 mg/kg, AHR ID50 = 1.4 mg/kg), whereas ULMW NAF-**heparin** (n = 7) was the most effective agent (ABR ID50 = 0.4 mg/kg, AHR ID50 = 0.2 mg/kg). ULMW NAF-**heparin** was 3.5 times more potent in attenuating antigen-induced AHR when administered "after" antigen challenge and failed to inhibit the bronchoconstrictor response to carbachol and histamine. In 15 additional sheep, segmental antigen challenge caused a marked increase in histamine in bronchoalveolar lavage fluid that was not prevented by any of the inhaled NAF-**heparins**. These data indicate that antiallergic activity of inhaled **heparin** is independent of its anticoagulant action and resides in the <2,500 ULMW chains. The antiallergic activity of NAF-**heparins** is mediated by an unknown biological action and may have therapeutic potential.

CT Check Tags: Animal
*Anti-Allergic Agents: PD, pharmacology
Ascaris suum: IM, immunology
*Bronchial Hyperreactivity: PP, physiopathology
Bronchoalveolar Lavage Fluid
*Bronchoconstriction: DE, drug effects
***Heparin, Low-Molecular-Weight: PD, pharmacology**
Histamine Release: DE, drug effects
Molecular Weight
Sheep

CN 0 (Anti-Allergic Agents); 0 (**Heparin**, Low-Molecular-Weight)

L122 ANSWER 5 OF 10 MEDLINE

AN 1998176784 MEDLINE

DN 98176784 PubMed ID: 9517607

TI Inhibition of antigen-induced airway hyperresponsiveness by ultralow molecular-weight **heparin**.

AU Molinari J F; Campo C; Shakir S; Ahmed T

CS Division of Pulmonary Diseases, University of Miami School of Medicine, Mount Sinai Medical Center, Miami Beach, Florida 33140, USA.

SO AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, (1998 Mar) 157 (3 Pt 1) 887-93.
Journal code: 9421642. ISSN: 1073-449X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199804

ED Entered STN: 19980416
Last Updated on STN: 19980416
Entered Medline: 19980407

AB Unfractionated **heparin** (UF-**heparin**) has been shown to prevent antigen-induced airway hyperresponsiveness (AHR), but it is ineffective when administered after the antigen challenge. We hypothesized that the failure of UF-**heparin** to modify postantigen AHR might depend on molecular weight. We therefore studied the effects of UF-**heparin** and three low-molecular-weight **heparin** fractions (**medium-molecular-weight heparin** [**MMWH**]; low-molecular-weight **heparin** [LMWH]; and ultralow-molecular-weight **heparin** [ULMWH]) on antigen-induced AHR and histamine release in bronchoalveolar lavage fluid (BALF). Specific lung resistance (SRL) was measured in 20 allergic sheep before, immediately after, and up to 2 h after challenge with Ascaris suum antigen. Airway responsiveness was expressed as the cumulative provocative

dose of carbachol, in breath units, that increased SRL by 400% (PD400). PD400 was determined before and 2 h after antigen, both without and after treatment with aerosolized UF-**heparin** (1,000 U/kg) and various **heparin** fractions (0.04 mg/kg to 5 mg/kg) administered after the antigen challenge. Inhaled UF-**heparin** (n = 4), **MMWH** (n = 4), and LMWH (n = 6) failed to modify postantigen AHR when administered after the challenge. Only ULMWH (n = 6) inhibited postantigen AHR in a dose-dependent manner (percent protection ranged from 31% to 139%). In eight additional sheep, histamine in BALF was measured with a radioimmunoassay (RIA) before and after the segmental antigen challenge, without and after pretreatment with inhaled UF-**heparin**, LMWH, or ULMWH. Inhaled UF-**heparin** and LMWH inhibited antigen-induced histamine release as measured in BALF by 81% and 75%, respectively; whereas ULMWH was ineffective in this respect. We conclude that: (1) modification of antigen-induced AHR by fractionated **heparins** is molecular-weight dependent; and (2) only ULMWH attenuates AHR when administered after antigen challenge, via an unknown mast-cell-independent action.

CT Check Tags: Animal
Administration, Inhalation
Aerosols
Airway Resistance: DE, drug effects
Anticoagulants: AD, administration & dosage
*Anticoagulants: TU, therapeutic use
***Antigens, Helminth: IM, immunology**
Ascaris suum: IM, immunology
Bronchial Hyperreactivity: IM, immunology
*Bronchial Hyperreactivity: PC, prevention & control
Bronchial Provocation Tests
Bronchoalveolar Lavage Fluid: CH, chemistry
Bronchoconstriction: DE, drug effects
Carbachol: DU, diagnostic use
Dose-Response Relationship, Drug
Heparin, Low-Molecular-Weight: AD, administration & dosage
***Heparin, Low-Molecular-Weight: TU, therapeutic use**
Histamine: AN, analysis
Histamine Release: DE, drug effects
Lung: DE, drug effects
Lung: IM, immunology
Mast Cells: IM, immunology
Molecular Weight
Muscarinic Agonists: DU, diagnostic use
Respiratory Hypersensitivity: IM, immunology
Sheep

RN 51-45-6 (Histamine); 51-83-2 (Carbachol)

CN 0 (Aerosols); 0 (Anticoagulants); 0 (Antigens, Helminth); 0 (**Heparin**, Low-Molecular-Weight); 0 (Muscarinic Agonists)

L122 ANSWER 6 OF 10 MEDLINE

AN 1998113608 MEDLINE

DN 98113608 PubMed ID: 9451639

TI Inhibition of allergic airway responses by inhaled low-molecular-weight **heparins**: molecular-weight dependence.

AU Martinez-Salas J; Mendelssohn R; Abraham W M; Hsiao B; Ahmed T

CS Division of Pulmonary Diseases, University of Miami School of Medicine, Mount Sinai Medical Center, Florida 33140, USA.

SO JOURNAL OF APPLIED PHYSIOLOGY, (1998 Jan) 84 (1) 222-8.
Journal code: 8502536. ISSN: 8750-7587.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 199803

ED Entered STN: 19980407
Last Updated on STN: 19980407
Entered Medline: 19980320

AB Inhaled **heparin** prevents antigen-induced bronchoconstriction and inhibits anti-immunoglobulin E-mediated mast cell degranulation. We hypothesized that the antiallergic action of **heparin** may be molecular weight dependent. Therefore, we studied the effects of three different low-molecular-weight fractions of **heparin** [**medium**-, low-, and ultralow-molecular-weight **heparin** (**MMWH**, LMWH, ULMWH, respectively)] on the antigen-induced acute bronchoconstrictor response (ABR) and airway hyperresponsiveness (AHR) in allergic sheep. Specific lung resistance was measured in 22 sheep before and after airway challenge with Ascaris suum antigen, without and after pretreatment with inhaled fractionated **heparins** at doses of 0.31-5.0 mg/kg. Airway responsiveness was estimated before and 2 h postantigen as the cumulative provocating dose of carbachol in breath units that increased specific lung resistance by 400%. All fractionated **heparins** caused a dose-dependent inhibition of ABR and AHR. ULMWH was the most effective fraction, with the inhibitory dose causing 50% protection (ID50) against ABR of 0.5 mg/kg, whereas ID50 values of LMWH and **MMWH** were 1.25 and 1.8 mg/kg, respectively. ULMWH was also the most effective fraction in attenuating AHR; the ID50 values for ULMWH, LMWH, and **MMWH** were 0.5, 2.5, and 4.7 mg/kg, respectively. These data suggest that 1) fractionated low-molecular-weight **heparins** attenuate antigen-induced ABR and AHR; 2) there is an inverse relationship between the antiallergic activity of **heparin** fractions and molecular weight; and 3) ULMWH is the most effective fraction preventing allergic bronchoconstriction and airway hyperresponsiveness.

CT Check Tags: Animal
Aerosols
Anticoagulants: AD, administration & dosage
Anticoagulants: CH, chemistry
*Anticoagulants: TU, therapeutic use
Ascaris: IM, immunology
Bronchial Hyperreactivity: DT, drug therapy
Heparin, Low-Molecular-Weight: AD, administration & dosage
Heparin, Low-Molecular-Weight: CH, chemistry
***Heparin, Low-Molecular-Weight: TU, therapeutic use**
Mast Cells: DE, drug effects
Mast Cells: ME, metabolism
Molecular Weight
*Respiratory Hypersensitivity: DT, drug therapy
Respiratory Hypersensitivity: PP, physiopathology
Respiratory Mechanics: DE, drug effects
Sheep

CN 0 (Aerosols); 0 (Anticoagulants); 0 (**Heparin**, Low-Molecular-Weight)

L122 ANSWER 7 OF 10 MEDLINE
AN 92311849 MEDLINE
DN 92311849 PubMed ID: 1319616
TI The mode of action of CY216 and CY222 in plasma.
AU Beguin S; Wielders S; Lormeau J C; Hemker H C
CS Department of Biochemistry, University of Limburg, Maastricht, The Netherlands.
SO THROMBOSIS AND HAEMOSTASIS, (1992 Jan 23) 67 (1) 33-41.
Journal code: 7608063. ISSN: 0340-6245.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199207
ED Entered STN: 19920807

Last Updated on STN: 19920807
Entered Medline: 19920724

AB Three fractions of the low molecular weight **heparin** CY216 (fraxiparin, mean molecular weight [**MMW**] 5,090), with **MMWs** of respectively, 3,090, 4,400 and 7,910 were prepared by gel permeation chromatography. From CY222 (**MMW** 3,770) as well as from CY216 and its three fractions the material with high affinity to antithrombin III (AT III) was obtained by chromatography on immobilised AT III. The molecular weight distribution of each of the ten preparations thus obtained was determined by high performance liquid chromatography, while the content of AT III binding material was determined by stoichiometric titration of AT III, monitored by intrinsic fluorescence enhancement. We measured the effect of all **heparins** on the decay of endogenous thrombin in plasma and on the overall generation of thrombin in plasma, triggered via the extrinsic or via the intrinsic pathway. From these data we calculated the time course of prothrombin conversion, i.e. the course of factor Xa activity as expressed by prothrombinase activity. It was found that in platelet-poor plasma the anticoagulant properties of the **heparins** are largely dependent on their antithrombin action, which is determined by their content of high affinity material with a MW of 5,400 or higher. The specific antithrombin activity of all **heparins**, when expressed in terms of material with high affinity to antithrombin III (HAM) with a MW greater than 5,400 is 13.0 min-1/(microgram/ml) (range 10.5-15.9).(ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Human; In Vitro
Antithrombin III: ME, metabolism
Antithrombins: PD, pharmacology
Heparin, Low-Molecular-Weight: BL, blood
Heparin, Low-Molecular-Weight: IP, isolation & purification
***Heparin, Low-Molecular-Weight: PD, pharmacology**
Molecular Weight
Prothrombin: ME, metabolism
***Thrombin: ME, metabolism**

RN 9000-94-6 (Antithrombin III); 9001-26-7 (Prothrombin)
CN 0 (Antithrombins); 0 (**Heparin**, Low-Molecular-Weight); EC 3.4.21.5 (Thrombin)

L122 ANSWER 8 OF 10 MEDLINE
AN 84155045 MEDLINE
DN 84155045 PubMed ID: 6704544
TI Elimination of high affinity **heparin** fractions and their anticoagulant and lipase activity.
AU de Swart C A; Nijmeyer B; Andersson L O; Holmer E; Verschoor L; Bouma B N; Sixma J J
SO BLOOD, (1984 Apr) 63 (4) 836-42.
Journal code: 7603509. ISSN: 0006-4971.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 198405
ED Entered STN: 19900319
Last Updated on STN: 19970203
Entered Medline: 19840504

AB High and low affinity **heparin** (HA and LA **heparin**) were prepared from commercial **heparin** by affinity chromatography to insolubilized antithrombin III. HA **heparin** was radiolabeled with 35S and subdivided by gel chromatography into high molecular weight (HMW, average 17,000-26,000 **daltons**), **intermediate** molecular weight (**MMW**, average 12,000-13,000 **daltons**), low molecular weight (LMW, average 5,000-7,000 **daltons**), and very low molecular weight (VLMW, average 4,600 **daltons**) fractions. The kinetics of lipolytic and anticoagulant activity and protein-bound

radioactivity were studied after intravenous injection of these fractions. LA **heparin** failed to induce anticoagulant activity but released the hepatic triglyceride lipase (H-TGL) and lipoprotein lipase (LPL) activities normally. VLMW and LMW **heparin** failed to release both lipolytic enzymes and did not induce anticoagulant activity measurable by the activated partial thromboplastin time (APTT). A powerful anticoagulant effect was found in the anti-Xa assay, which disappeared according to a continuously concave curve in semilogarithmic plots, with elimination rates similar to those of the protein-bound radiolabel. The other **heparin** preparations induced all activities measured. **Heparin** anticoagulant activity estimated by the two assays disappeared following a convex curve, preceded by a rapid initial elimination phase in semilogarithmic plots. The disappearance rates of plasma protein-bound **heparin** radioactivity and **heparin** anticoagulant activity estimated by factor Xa inactivation were similar. Peak values of the two lipolytic activities were attained rapidly. H- TGL activity, as well as LPL activity, disappeared following convex curves in semilogarithmic plots, with elimination rates similar to those of plasma protein-bound **heparin** radioactivity. On the basis of these kinetics, we suggest that, after intravenous administration of **heparin**, the two lipolytic enzymes present in plasma are complexed with **heparin**, analogous to the **heparin**-antithrombin III complex. Finally, the kinetic data indicate that elimination of these activities is determined by the **heparin** part of the complexes, probably by removal of free **heparin**.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adult
*Anticoagulants: BL, blood
Blood Proteins: ME, metabolism
Chromatography, Affinity
Factor X: AI, antagonists & inhibitors
Factor Xa
Fractionation
***Heparin: BL, blood**
Heparin: PD, pharmacology
Kinetics
***Lipase: BL, blood**
Lipolysis: DE, drug effects
Molecular Weight
Partial Thromboplastin Time
Protein Binding

RN 9001-29-0 (Factor X); **9005-49-6 (Heparin)**
CN 0 (Anticoagulants); 0 (Blood Proteins); EC 3.1.1.3 (Lipase); EC 3.4.21.6 (Factor Xa)

L122 ANSWER 9 OF 10 MEDLINE
AN 83093890 MEDLINE
DN 83093890 PubMed ID: 7179225
TI Enhancement by **heparin** of thrombin-induced antithrombin III proteolysis: its relation to the molecular weight and anticoagulant activity of **heparin**.
AU Marciniak E; Gora-Maslak G
NC HL 26136 (NHLBI)
SO THROMBOSIS RESEARCH, (1982 Nov 1) 28 (3) 411-21.
Journal code: 0326377. ISSN: 0049-3848.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198302
ED Entered STN: 19900317
Last Updated on STN: 19970203
Entered Medline: 19830225

AB Previous findings indicated that binding of **heparin** to antithrombin III (AT III) facilitates thrombin-induced proteolysis of the inhibitor. We now studied this property of **heparin** in regard to its molecular weight and anticoagulant activity. Commercial **heparin** was resolved on Sephadex G-200 into six fractions of decreasing molecular weight. From each fraction high affinity (HA) **heparin** was isolated by chromatography on AT III-Sepharose and examined in reaction of alpha-thrombin with a molar excess of 125I AT III. Proteolysis of the inhibitor was assessed by SDS polyacrylamide gel electrophoresis. In the presence of the HA **heparin** from 18% to 38% of AT III participating in reaction appeared in the form of inactive 50,000-**dalton** fragment, as opposed to 7% of AT III fragmented in the absence of **heparin**. Although the ability to potentiate proteolysis was at its peak in the **medium-molecular-size heparin** fraction, the amount of degraded inhibitor relative to anticoagulant activity increased with decreasing molecular weight of the polysaccharide. These findings are consistent with the possibility that the ability of bound **heparin** to facilitate the cleavage of AT III by thrombin is generally less contingent upon secondary characteristics of the polysaccharide than the anticoagulant activity.

CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
***Antithrombin III: ME, metabolism**
Chromatography, Gel
Drug Synergism
Electrophoresis, Polyacrylamide Gel
Fractionation
***Heparin: PD, pharmacology**
Iodine Radioisotopes
Molecular Weight
Protein Binding
Thrombin: PD, pharmacology

RN 9000-94-6 (Antithrombin III); **9005-49-6 (Heparin)**
CN 0 (Iodine Radioisotopes); EC 3.4.21.5 (Thrombin)

L122 ANSWER 10 OF 10 MEDLINE
AN 82045435 MEDLINE
DN 82045435 PubMed ID: 7295101
TI Platelet function as an assay for uremic toxins.
AU Lindsay R M; Dennis B N; Bergstrom J C; Jonsson C; Furst P
SO ARTIFICIAL ORGANS, (1981) 4 Suppl 82-9.
Journal code: 7802778. ISSN: 0160-564X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198112
ED Entered STN: 19900316
Last Updated on STN: 19900316
Entered Medline: 19811221

AB The nature of the toxins responsible for the uremic syndrome remains a mystery. There is current interest, however, in the possible role of **middle molecular weight** (500-3000 **daltons**) retention products and elevated hormonal factors, e.g., parathormone, as such toxins. Clinical studies of the uremic platelet defect suggest that this defect is due to a dialysable platelet inhibitor perhaps within the **middle molecular weight** range. An in vitro test system has been developed using the response of platelets in plasma, or in buffer following separation by gel-filtration, to release 14C labelled serotonin by graded doses of particulate collagen. This can demonstrate reversible and irreversible platelet inhibition by exogenous factors such as drugs, and in addition, demonstrates a reversible platelet inhibitor in uremic patients. It is suggested, therefore, this gel-filtered platelet preparation may be useful to study,

biologically, the toxicity of **middle** molecules and other factors. Preliminary experimental work demonstrates that following the fractionation of an ultrafiltrate from uremic serum an inhibitor of platelet release is found in two cases: (1) in those fractions containing substances in the **middle** molecular range; and (2) in association with those fractions where the salt peak exists. In fractions obtained from ultrafiltrates of normal serum, platelet toxicity only coincides with the salt peak. These experiments do, indeed, support a toxic role for **middle** molecules but, in addition, indicate some of the problems of bioassays and the need for careful controls.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Blood Platelets: DE, drug effects
***Blood Platelets: PH, physiology**
Collagen: PD, pharmacology
Creatinine: BL, blood
Heparin: PD, pharmacology
Reference Values
Serotonin: BL, blood
***Toxins: BL, blood**
Toxins: PD, pharmacology
Uremia: PP, physiopathology

RN 50-67-9 (Serotonin); 60-27-5 (Creatinine); **9005-49-6 (Heparin)**; 9007-34-5 (Collagen)

CN 0 (Toxins); 0 (uremia **middle** molecule toxins)

=> fil reg
FILE 'REGISTRY' ENTERED AT 14:09:27 ON 28 JAN 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 27 JAN 2003 HIGHEST RN 482277-90-7
DICTIONARY FILE UPDATES: 27 JAN 2003 HIGHEST RN 482277-90-7

TSCA INFORMATION NOW CURRENT THROUGH MAY 20, 2002

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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

=> d ide can tot l123

L123 ANSWER 1 OF 5 REGISTRY COPYRIGHT 2003 ACS
RN **9041-08-1** REGISTRY
CN Heparin, sodium salt (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Alfa 87-120
CN Alfa 87-163
CN Alfa 87-198
CN Alfa 87-81
CN Alfa 88-247
CN Ardeparin sodium
CN Bemiparin sodium

CN Clexan
CN Dalteparin sodium
CN Deligoparin sodium
CN Depo-Heparin
CN Enoxaparin sodium
CN Fragmin
CN Fragmin IV
CN H 2149
CN Hed-Heparin
CN Hepalean
CN Heparin sodium
CN Hepathrom
CN Inno-Hep
CN Kabi 2165
CN LHN 1
CN Lioton 1000
CN Liquaemin sodium
CN Liquemin
CN Logiparin
CN Lovenox
CN Minolteparin sodium
CN Normiflo
CN OP 2000
CN Parnaparin sodium
CN PK 10169
CN Pularin
CN Reviparin sodium
CN RO 11
CN RP 54563
CN Sodium acid heparin
CN Sodium heparin
CN Sodium heparinate
CN Tinzaparin sodium
CN WY 90493RD
DR 12656-11-0, 101921-26-0, 102785-31-9
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration, Polyester, Polyester formed
LC STN Files: ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CAPLUS, CBNB, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
1029 REFERENCES IN FILE CA (1962 TO DATE)
78 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
1033 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:61397

REFERENCE 2: 138:61375

REFERENCE 3: 138:49698

REFERENCE 4: 138:33098

REFERENCE 5: 138:11261

REFERENCE 6: 138:1961

REFERENCE 7: 138:221

REFERENCE 8: 137:379827

REFERENCE 9: 137:362797

REFERENCE 10: 137:345806

L123 ANSWER 2 OF 5 REGISTRY COPYRIGHT 2003 ACS
RN **9005-49-6** REGISTRY
CN Heparin (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN .alpha.-Heparin
CN Bemiparin
CN Certoparin
CN Clexane
CN Clivarin
CN Clivarine
CN CY 216
CN CY 222
CN Dalteparin
CN Enoxaparin
CN Fluxum
CN FR 860
CN Fragmin A
CN Fragmin B
CN Fraxiparin
CN Heparin subcutan
CN Heparin sulfate
CN Heparinic acid
CN KB 101
CN Multiparin
CN Novoheparin
CN OP 386
CN OP 622
CN Pabyrn
CN Parnaparin
CN Parvoparin
CN Reviparin
CN Sandoparin
CN Sublingula
CN Tinzaparin
CN Vetren
CN Vitrum AB
DR 9075-96-1, 11078-24-3, 11129-39-8, 104521-37-1, 37324-73-5, 91449-79-5
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration, Polyester, Polyester formed
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PHAR, PHARMASEARCH, PIRA, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
19732 REFERENCES IN FILE CA (1962 TO DATE)
1875 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19751 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:63051

REFERENCE 2: 138:61397

REFERENCE 3: 138:61389

REFERENCE 4: 138:61375

REFERENCE 5: 138:61345

REFERENCE 6: 138:61340

REFERENCE 7: 138:61269

REFERENCE 8: 138:54187

REFERENCE 9: 138:52352

REFERENCE 10: 138:52268

L123 ANSWER 3 OF 5 REGISTRY COPYRIGHT 2003 ACS
RN **9002-05-5** REGISTRY
CN Blood-coagulation factor Xa (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Activated blood-coagulation factor X
CN Autoprothrombin C
CN Blood factor Xa
CN Coagulation factor Xa
CN E.C. 3.4.21.6
CN Factor Xa
CN Plasma thromboplastin
CN Prothrombinase
CN Thrombokinase
CN Thrombomat
CN Thromboplastin
CN Thromboplastin, plasma
DR 11129-03-6, 87912-91-2
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DIOGENES, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, NIOSHTIC, PROMT, TOXCENTER, USAN, USPAT2, USPATFULL
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
3369 REFERENCES IN FILE CA (1962 TO DATE)
97 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3376 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:56212

REFERENCE 2: 138:55979

REFERENCE 3: 138:51876

REFERENCE 4: 138:51520

REFERENCE 5: 138:49697

REFERENCE 6: 138:49676

REFERENCE 7: 138:49664

REFERENCE 8: 138:49645

REFERENCE 9: 138:49640

REFERENCE 10: 138:49368

L123 ANSWER 4 OF 5 REGISTRY COPYRIGHT 2003 ACS
RN **9002-04-4** REGISTRY
CN Thrombin (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN Blood-coagulation factor II, activated
CN Blood-coagulation factor IIa
CN E.C. 3.4.21.5
CN E.C. 3.4.4.13
CN Factor IIa
CN Thrombase
CN Thrombin JMI
CN Thrombin-C
CN Thrombofort
CN Thrombostat
CN Topical
CN Tropostasin
DR 8050-02-0, 8059-56-1, 9014-41-9, 105881-84-3, 53028-63-0
MF Unspecified
CI COM, MAN
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, NIOSHTIC, PIRA, PROMT, RTECS*, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
14903 REFERENCES IN FILE CA (1962 TO DATE)
745 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
14917 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:55979

REFERENCE 2: 138:53332

REFERENCE 3: 138:52368

REFERENCE 4: 138:51887

REFERENCE 5: 138:51830

REFERENCE 6: 138:51644

REFERENCE 7: 138:51520

REFERENCE 8: 138:50092

REFERENCE 9: 138:49697

REFERENCE 10: 138:49689

L123 ANSWER 5 OF 5 REGISTRY COPYRIGHT 2003 ACS

RN 9000-94-6 REGISTRY
CN **Antithrombin (9CI)** (CA INDEX NAME)
OTHER NAMES:
CN Antithrombin III
CN Heparin cofactor
CN Heparin cofactor B
CN Org 10849
CN Thrombin inhibitor
AR 90170-80-2
DR 9041-91-2, 52014-67-2
MF Unspecified
CI PMS, COM, MAN
PCT Manual registration
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, CBNB, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MSDS-OHS, NIOSHTIC, PHAR, PHARMASEARCH, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: EINECS**
(**Enter CHEMLIST File for up-to-date regulatory information)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
4793 REFERENCES IN FILE CA (1962 TO DATE)
509 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
4803 REFERENCES IN FILE CAPLUS (1962 TO DATE)

REFERENCE 1: 138:61368

REFERENCE 2: 138:53691

REFERENCE 3: 138:49699

REFERENCE 4: 138:49283

REFERENCE 5: 138:37880

REFERENCE 6: 138:37404

REFERENCE 7: 138:36566

REFERENCE 8: 138:32939

REFERENCE 9: 138:32641

REFERENCE 10: 138:23134

=> fil wpix
FILE 'WPIX' ENTERED AT 14:27:19 ON 28 JAN 2003

FILE LAST UPDATED: 24 JAN 2003 <20030124/UP>
MOST RECENT DERWENT UPDATE: 200306 <200306/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

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/BIX is also provided which comprises both /BI and /ABEX <<<

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GUIDES, PLEASE VISIT:
http://www.derwent.com/userguides/dwpi_guide.html <<<

=> d l139 all abeq tech abex tot

L139 ANSWER 1 OF 2 WPIX (C) 2003 THOMSON DERWENT
AN 2001-476023 [51] WPIX
DNC C2001-142786
TI New **medium molecular weight heparin**
having high therapeutic index, obtained by controlled depolymerization
with nitrous acid, useful e.g. for treating or preventing thromboembolic
disease or myocardial infarction.
DC B04
IN WELZEL, D
PA (WELZ-I) WELZEL D
CYC 95
PI WO 2001051525 A1 20010719 (200151)* DE 34p C08B037-10 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2001030019 A 20010724 (200166) C08B037-10 <--
EP 1252194 A1 20021030 (200279) DE C08B037-10 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
RO SE SI TR
ADT WO 2001051525 A1 WO 2000-DE4674 20001222; AU 2001030019 A AU 2001-30019
20001222; EP 1252194 A1 EP 2000-990588 20001222, WO 2000-DE4674 20001222
FDT AU 2001030019 A Based on WO 200151525; EP 1252194 A1 Based on WO 200151525
PRAI DE 2000-10000602 20000110
IC ICM **C08B037-10**
ICS **A61K031-727**
AB WO 200151525 A UPAB: 20010910
NOVELTY - **Heparin** (I) having an average molecular weight of
10-11.5 (preferably 10.5) kd is new.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the
preparation of (I).
ACTIVITY - Anticoagulant; thrombolytic; cardiant; antianginal.
MECHANISM OF ACTION - Factor Xa antagonist; factor IIa antagonist;
thrombin inhibitor.
(I) has anti-Factor Xa activity 174.9 IU/mg and anti-Factor IIa
activity 170.0 IU/mg, the corresponding values for Enoxoparin (RTM; low
molecular **heparin**) being 100.0 IU/mg and 26.3 IU/mg and for
Liquemin (RTM; un-fractionated **heparin**) 159.0 IU/mg and 159.0
IU/mg.
USE - (I) is used for the prophylaxis and therapy of thromboembolic

processes, therapy of acute myocardial infarction or unstable angina or inhibition of coagulation in extracorporeal circuits (all claimed).

ADVANTAGE - (I) has an optimum combination of activity and tolerance properties relative to un-fractionated **heparin** (UFH) or low molecular weight **heparin** (LMH). In particular (I) has strong anticoagulant activity, significantly higher anti-Factor Xa and anti-Factor IIa activity than UFH or LMH, a low tendency to cause bleeding (as demonstrated by template bleeding time tests in rabbits) and a high therapeutic index (e.g. 2.24 times higher than that of LMH).

Dwg.0/8

FS CPI

FA AB; DCN

MC CPI: **B04-C02E1**; B14-F01B; B14-F01D; B14-F04

TECH UPTX: 20010910

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) is obtained by controlled depolymerization of un-fractionated **heparin** with nitrous acid, followed by molecular filtration.

ABEX

ADMINISTRATION - (I) is specifically administered parenterally (claimed). No dosage ranges are given.

EXAMPLE - No preparative examples are given.

L139 ANSWER 2 OF 2 WPIX (C) 2003 THOMSON DERWENT

AN 2001-147075 [15] WPIX

DNC C2001-043453

TI **Medium molecular weight heparin**

composition, used for the treatment of thrombotic conditions e.g. deep vein thrombosis, comprises a mixture of sulfated oligosaccharides having a molecular weight of 6000-12000 Da.

DC A11 A96 B04

IN HIRSH, J; WEITZ, J I

PA (HAMI-N) HAMILTON CIVIC HOSPITALS RES DEV INC; (WEIT-I) WEITZ J I

CYC 95

PI WO 2001002443 A1 20010111 (200115)* EN 82p C08B037-10 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000056682 A 20010122 (200125) C08B037-10 <--
EP 1192187 A1 20020403 (200230) EN C08B037-10 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 2000012202 A 20020402 (200231) C08B037-10 <--
CZ 2001004665 A3 20020515 (200241) C08B037-10 <--
KR 2002032444 A 20020503 (200270) A61K031-727 <--
HU 2002001712 A2 20021028 (200277) C08B037-10 <--
CN 1371391 A 20020925 (200305) C08B037-10 <--

ADT WO 2001002443 A1 WO 2000-CA774 20000629; AU 2000056682 A AU 2000-56682 20000629; EP 1192187 A1 EP 2000-941847 20000629, WO 2000-CA774 20000629; BR 2000012202 A BR 2000-12202 20000629, WO 2000-CA774 20000629; CZ 2001004665 A3 WO 2000-CA774 20000629, CZ 2001-4665 20000629; KR 2002032444 A KR 2001-716877 20011228; HU 2002001712 A2 WO 2000-CA774 20000629, HU 2002-1712 20000629; CN 1371391 A CN 2000-812090 20000629

FDT AU 2000056682 A Based on WO 200102443; EP 1192187 A1 Based on WO 200102443; BR 2000012202 A Based on WO 200102443; CZ 2001004665 A3 Based on WO 200102443; HU 2002001712 A2 Based on WO 200102443

PRAI US 1999-154744P 19990917; US 1999-141865P 19990630

IC ICM **A61K031-727**; **C08B037-10**
ICS A61P007-02

AB WO 200102443 A UPAB: 20010317

NOVELTY - **Medium molecular weight heparin** (**MMWH**) composition comprises a mixture of sulfated oligosaccharides having a molecular weight of 6000-12000 Da.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a **medium molecular weight heparin** (MMWH2) composition comprising a mixture of oligosaccharides derived from **heparin**, and having the following characteristics:

(a) antithrombin and **heparin** cofactor II (HCII) related anticoagulant activity in vitro;

(b) oligosaccharides which are too short to bridge thrombin to fibrin, but long enough to bridge antithrombin or HCII to thrombin;

(c) at least 15, 20, 25, 30, 35, or 40 % of the oligosaccharides having at least one or more pentasaccharide sequence;

(d) enriched with oligosaccharides of molecular weight ranges 6000-11000, 7000-10000, 7500-10000, 7800-10000, 7800-9800, 7800-9600 or 8000-9600 Da;

(e) oligosaccharides having a mean molecular weight of 7800-10000 (preferably 7800-9800, especially 8000-9800) Da;

(f) at least 30, 35, 40, 45, or 50 % of the oligosaccharides have a molecular weight of at least 6000 (preferably at least 8000) Da;

(g) a polydispersity of 1.1-1.5 (preferably 1.2-1.4, especially 1.3);

(h) similar anti-factor Xa and anti-factor IIa activities, preferably in a ratio of anti-factor Xa to anti-factor IIa activity of 2:1-1:1, especially 1.5:1-1:1;

(i) an anti-factor Xa activity of 80-155 (preferably 90-130 (especially 100-110) IU/mg and/or

(j) an anti-factor IIa activity of 20-150 (preferably 40-100 (especially 90-100) IU/mg; and

(2) the preparation of a **MMWH** composition comprising:

(i) subjecting unfractionated **heparin** to a limited periodate oxidation reaction such that only iduronic acids of the unfractionated **heparin** are oxidized;

(ii) subjecting the oxidized unfractionated **heparin** to alkaline hydrolysis; and

(iii) recovering the **MMWH** composition, containing a mixture of sulfated oligosaccharides having a molecular weight of 8000-12000 Da.

ACTIVITY - Thrombolytic; anticoagulant; antiatherosclerotic; cardiant.

A study was carried out to compare the efficacy of **MMWH** and LMWH in the treatment of deep vein thrombosis in rabbits. Twenty four New Zealand White male rabbits underwent surgery which introduced a thrombectomy catheter into the jugular vein. Four centimeters of the jugular vein was damaged by 15 passages of inflated balloon catheter. Clots were then induced using 1 micro Ci of I125-labelled rabbit fibrinogen. Twenty five minutes into thrombus maturation the rabbits received: (a) sterile saline (1 ml); (b) LMWH (1 mg/kg or 3 mg/kg); or (c) **MMWH** (V-21; 1 mg/kg or 3 mg/kg). Blood was collected prior to surgery, and then after 5 minutes, and then after 1, 3, 6, 9, 12, and 24 hours after clot maturation. The results are shown in the figure.

MECHANISM OF ACTION - Factor Xa inhibitor; factor IIa inhibitor.

USE - The **MMWH** compositions are used in the treatment of thrombotic conditions such as arterial thrombosis, coronary artery thrombosis, venous thrombosis or pulmonary embolism. The **MMWH** compositions are also used for the prevention of thrombus formation in patients at risk of developing thrombosis, such as patients who have undergone a medical procedure, such as cardiac surgery, cardiopulmonary bypass, catheterization or atherectomy, or patients suffering from a medical condition which disrupts hemostasis, e.g. coronary artery disease or atherosclerosis. The **MMWH** compositions may also be used for the treatment of deep vein thrombosis in patients who have undergone orthopedic surgery (all claimed).

ADVANTAGE - The **heparin** chains are too short to bridge thrombin to fibrin, but are long enough to bridge antithrombin to thrombin. The **MMWH** compositions inhibit fibrin-bound thrombin and fluid-phase thrombin equally well.
Dwg.0/41
FS CPI
FA AB; DCN
MC CPI: A03-A01; A10-E24; A12-V01; **B04-C02E1**; B04-C02X; B14-F02; B14-F04; B14-F07
TECH UPTX: 20010317
TECHNOLOGY FOCUS - POLYMERS - Preferred Composition: The composition inhibits fibrin-bound thrombin and fluid-phase thrombin by catalyzing antithrombin, and inhibits thrombin generated by catalyzing factor Xa by antithrombin. The composition has an anti-factor IIa activity of 40 -100 (preferably 60-75, especially 65) U/mg, and an anti-factor Xa activity of 90-150 (preferably 100-125, especially 115) U/mg. The sulfated oligosaccharides have molecular weights of 8000-10000 (preferably 9000) Da. At least 31 % of the sulfated oligosaccharides have a molecular weight at least 7800 Da. At least 25 % of the sulfated oligosaccharides have a molecular weight of at least 10000 Da. The MMWH2 composition has characteristics:
(1) (a), (b), (c) and (e);
(2) (b), (c), (e) and (g);
(3) (b)-(e) and (h);
(4) (b)-(d) and (g);
(5) (b), (e), (i) and (j);
(6) (b), (e)-(g), (i) and (j); or
(7) (a)-(j).
The MMWH2 composition is derived from **heparinase** depolymerization or nitrous acid depolymerization of unfractionated **heparin**.
ABEX
ADMINISTRATION - Administration is by injection (claimed), e.g. intravenous, subcutaneous or intramuscular.
Dosage is 2-200 (preferably 5-50) microgram/day.

EXAMPLE - **Heparin** (100 g) was treated using limited periodate/hydrolysis conditions, 7 mM sodium periodate, and purified by gel-filtration chromatography. A final product was obtained (30 mg) having oligosaccharides of molecular weight 6000-12000 Da, with a peak molecular weight at 9000 Da.

=> fil wpix
FILE 'WPIX' ENTERED AT 14:28:57 ON 28 JAN 2003

FILE LAST UPDATED: 24 JAN 2003 <20030124/UP>
MOST RECENT DERWENT UPDATE: 200306 <200306/DW>
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    PLEASE VISIT:
 http://www.stn-international.de/training_center/patents/stn_guide.pdf <<<

>>> FOR INFORMATION ON ALL DERWENT WORLD PATENTS INDEX USER
    GUIDES, PLEASE VISIT:
    http://www.derwent.com/userguides/dwpi_guide.html <<<

=> fil dpci
FILE 'DPCI' ENTERED AT 14:29:05 ON 28 JAN 2003
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FILE LAST UPDATED: 20 JAN 2003       <20030120/UP>
PATENTS CITATION INDEX, COVERS 1973 TO DATE

>>>  LEARNING FILE LDPCI AVAILABLE  <<<

=> d all


L145 ANSWER 1 OF 1  DPCI  (C) 2003 THOMSON DERWENT
AN   2001-147075 [15]   DPCI
DNC  C2001-043453
TI   Medium molecular weight heparin composition, used for the treatment of
     thrombotic conditions e.g. deep vein thrombosis, comprises a mixture of
     sulfated oligosaccharides having a molecular weight of 6000-12000 Da.
DC   A11 A96 B04
IN   HIRSH, J; WEITZ, J I
PA   (HAMI-N) HAMILTON CIVIC HOSPITALS RES DEV INC; (WEIT-I) WEITZ J I
CYC  95
PI   WO 2001002443 A1 20010111 (200115)* EN   82p    C08B037-10       <--
        RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
            NL OA PT SD SE SL SZ TZ UG ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
            DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
            LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
            SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
     AU 2000056682 A  20010122 (200125)              C08B037-10
     EP 1192187    A1 20020403 (200230)  EN          C08B037-10
         R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT
            RO SE SI
     BR 2000012202 A  20020402 (200231)              C08B037-10
     CZ 2001004665 A3 20020515 (200241)              C08B037-10
     KR 2002032444 A  20020503 (200270)              A61K031-727
     HU 2002001712 A2 20021028 (200277)              C08B037-10
     CN 1371391    A  20020925 (200305)              C08B037-10
ADT  WO 2001002443 A1 WO 2000-CA774 20000629; AU 2000056682 A AU 2000-56682
     20000629; EP 1192187 A1 EP 2000-941847 20000629, WO 2000-CA774 20000629;
     BR 2000012202 A BR 2000-12202 20000629, WO 2000-CA774 20000629; CZ
     2001004665 A3 WO 2000-CA774 20000629, CZ 2001-4665 20000629; KR 2002032444
     A KR 2001-716877 20011228; HU 2002001712 A2 WO 2000-CA774 20000629, HU
     2002-1712 20000629; CN 1371391 A CN 2000-812090 20000629
FDT  AU 2000056682 A Based on WO 200102443; EP 1192187 A1 Based on WO
     200102443; BR 2000012202 A Based on WO 200102443; CZ 2001004665 A3 Based
     on WO 200102443; HU 2002001712 A2 Based on WO 200102443
PRAI US 1999-154744P  19990917; US 1999-141865P  19990630
IC   ICM  A61K031-727; C08B037-10
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ICS A61P007-02
FS CPI

CTCS CITATION COUNTERS

PNC.DI	0	Cited Patents Count (by inventor)
PNC.DX	4	Cited Patents Count (by examiner)
IAC.DI	0	Cited Issuing Authority Count (by inventor)
IAC.DX	2	Cited Issuing Authority Count (by examiner)
PNC.GI	0	Citing Patents Count (by inventor)
PNC.GX	0	Citing Patents Count (by examiner)
IAC.GI	0	Citing Issuing Authority Count (by inventor)
IAC.GX	0	Citing Issuing Authority Count (by examiner)
CRC.I	0	Cited Literature References Count (by inventor)
CRC.X	1	Cited Literature References Count (by examiner)

CDP CITED PATENTS UPD: 20020206

Cited by Examiner

CITING PATENT	CAT	CITED PATENT	ACCNO
WO 200102443 A	A	EP 101141	A 1984-049439/08
	PA:	(PHAA) PHARMACIA & UPJOHN; (HEPA-N) HEPAR INDS INC	
	IN:	AMAYA, E; FUSSI, F; SMITH, M R	
	A	EP 244235	A 1987-308455/44
	PA:	(NOVO) NOVO IND AS; (NOVO) NOVO-NORDISK AS	
	IN:	NIELSEN, J I	
	A	WO 9218545	A 1992-382054/46
	PA:	(KABI) KABI PHARMACIA AB; (PHAA) PHARMACIA & UPJOHN AB; (PHAA) PHARMACIA AB	
	IN:	MATTSSON, C; SVAHN, C; WEBER, M; MATTSSON, C J; SVAHN, C M E; WEBER, M P	
	A	WO 9855515	A 1999-080826/07
	PA:	(HAMI-N) HAMILTON CIVIC HOSPITALS RES DEV INC	
	IN:	HIRSH, J; WEITZ, J; WEITZ, J I	

REN LITERATURE CITATIONS UPR: 20020206

Citations by Examiner

CITING PATENT	CAT	CITED LITERATURE
WO 200102443 A		LARS-AKE FRANSSON ET AL.: "Periodate oxidation and alkaline degradation of heparin-related glycans." CARBOHYDRATE RESEARCH, vol. 80, 1980, pages 131-145, XP002151018

=> d all abeq tech abex tot

L147 ANSWER 1 OF 4 WPIX (C) 2003 THOMSON DERWENT
AN 1999-080826 [07] WPIX
DNC C1999-024196
TI Modified low molecular weight heparin antithrombotic agent - inacivates fibrin bound thrombin, and blocks thrombin generation, prevents reactivation of coagulation on treatment cessation.

DC B03 B04
IN HIRSH, J; WEITZ, J; WEITZ, J I
PA (HAMI-N) HAMILTON CIVIC HOSPITALS RES DEV INC
CYC 83
PI WO 9855515 A1 19981210 (199907)* EN 50p C08B037-10 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM GW HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9877538 A 19981221 (199919) C08B037-10
EP 986581 A1 20000322 (200019) EN C08B037-10
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
US 6075013 A 20000613 (200035) A61K031-725
US 2001046974 A1 20011129 (200202) A61K031-727
ADT WO 9855515 A1 WO 1998-CA548 19980605; AU 9877538 A AU 1998-77538 19980605; EP 986581 A1 EP 1998-925356 19980605, WO 1998-CA548 19980605; US 6075013 A Provisional US 1997-72098P 19970606, US 1998-92325 19980605; US 2001046974 A1 Provisional US 1997-72098P 19970606, Cont of US 2000-445215 20000504, US 2001-874009 20010606
FDT AU 9877538 A Based on WO 9855515; EP 986581 A1 Based on WO 9855515
PRAI US 1997-72098P 19970606; US 1998-92325 19980605; US 2000-445215 20000504; US 2001-874009 20010606
IC ICM A61K031-725; A61K031-727; C08B037-10
ICS A61K031-725
AB WO 9855515 A UPAB: 19990224
Modified low molecular weight heparin (I) having a molecular weight of about 5-9 kiloDaltons (kD), is new.

USE - (I) is of use in thrombotic conditions, or where there is a risk of thrombosis, as in treatment and prevention of cardiovascular disorders, including angina, myocardial infarction, stroke, pulmonary embolism, and deep vein or arterial thrombosis. It is also used in medical procedures in which there is risk of thrombus generation, including cardiac surgery (e.g., cardiopulmonary bypass), catheterisation (e.g., cardiac catheterisation, percutaneous transluminal coronary angioplasty), atherectomy, or placement of a prosthetic device, as for cardiovascular valves, vascular grafts, and stents. (I) is also used for extracorporeal circulation in patients undergoing renal dialysis.

ADVANTAGE - (I) has shorter heparin type chains than heparin itself; they are too short to bridge thrombin to fibrin, but are long enough to bridge antithrombin to fibrin. Therefore, unlike heparin itself, (I) inactivates both fibrin bound thrombin and fluid phase free thrombin, as well as factor IIa and Xa inactivation by antithrombin. On the other hand, (I) has longer chains than prior art low molecular weight heparin (LMWH), which are not long enough to bridge antithrombin to thrombin. The other type of compounds tried, the direct thrombin inhibitors, as typified by hirudin and hirulog, do not block thrombin generation, and act generally in stoichiometric quantities, so that high concentrations are required, particularly at surfaces.

Dwg.11/13
FS CPI
FA AB; GI; DCN
MC CPI: B04-C02E1; B14-F01B; B14-F01D; B14-F04; B14-N16

L147 ANSWER 2 OF 4 WPIX (C) 2003 THOMSON DERWENT
AN 1992-382054 [46] WPIX
DNC C1992-169522
TI New bovine and porcine-derived heparin derivs. - for treatment of ischaemic heart diseases and related vascular disorders and to enhance development of coronary collateral perfusion.
DC B04
IN MATTSSON, C; SVAHN, C; WEBER, M; MATTSSON, C J; SVAHN, C M E; WEBER, M P

PA (KABI) KABI PHARMACIA AB; (PHAA) PHARMACIA & UPJOHN AB; (PHAA) PHARMACIA AB
CYC 19
PI WO 9218545 A1 19921029 (199246)* EN 34p C08B037-10 <--
RW: AT BE CH DE DK ES FR GB GR IT LU MC NL SE
W: AU CA JP US
AU 9216463 A 19921117 (199310) C08B037-10
EP 536363 A1 19930414 (199315) EN 34p C08B037-10
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
AU 642626 B 19931021 (199349) C08B037-10
JP 05508184 W 19931118 (199351) C08B037-10
EP 536363 B1 19970618 (199729) EN 24p C08B037-10
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE
DE 69220442 E 19970724 (199735) C08B037-10
ES 2104909 T3 19971016 (199748) C08B037-10
US 6150342 A 20001121 (200101) A01N043-04
US 6326476 B1 20011204 (200203) C08B037-10
JP 3278676 B2 20020430 (200230) 14p C08B037-10
ADT WO 9218545 A1 WO 1992-SE243 19920414; AU 9216463 A AU 1992-16463 19920414, WO 1992-SE243 19920414; EP 536363 A1 EP 1992-908867 19920414, WO 1992-SE243 19920414; AU 642626 B AU 1992-16463 19920414; JP 05508184 W JP 1992-508099 19920414, WO 1992-SE243 19920414; EP 536363 B1 EP 1992-908867 19920414, WO 1992-SE243 19920414; DE 69220442 E DE 1992-620442 19920414, EP 1992-908867 19920414, WO 1992-SE243 19920414; ES 2104909 T3 EP 1992-908867 19920414; US 6150342 A WO 1992-SE243 19920414, US 1992-949551 19921119; US 6326476 B1 Cont of WO 1992-SE243 19920414, Cont of US 1992-949551 19921119, US 1995-438933 19950510; JP 3278676 B2 JP 1992-508099 19920414, WO 1992-SE243 19920414
FDT AU 9216463 A Based on WO 9218545; EP 536363 A1 Based on WO 9218545; AU 642626 B Previous Publ. AU 9216463, Based on WO 9218545; JP 05508184 W Based on WO 9218545; EP 536363 B1 Based on WO 9218545; DE 69220442 E Based on EP 536363, Based on WO 9218545; ES 2104909 T3 Based on EP 536363; US 6150342 A Based on WO 9218545; US 6326476 B1 Cont of US 6150342; JP 3278676 B2 Previous Publ. JP 05508184, Based on WO 9218545
PRAI SE 1991-1155 19910418
REP 6.Jnl.Ref; EP 14184; EP 27089; EP 287477; 3.Jnl.Ref
IC ICM A01N043-04; C08B037-10
ICS A61K031-715; A61K031-725; A61K031-727; A61K037-10; A61P009-10
AB WO 9218545 A UPAB: 20020221
New heparin derivs. (I) from bovine or porcine heparin are characterised by (a) a molecular weight equal to or larger than the standard heparin; (b) a sulphur content equal to or higher than that of the starting heparin or at least 13% w.w; (c) an anticoagulant activity in the anti-FXa assay of less than 10% of the standard heparin they are made from: (d) a ratio of APTT activity over anti-FXa activity of 3-35; (e) a reduced prolongation of bleeding time compared to the standard heparin thye are made from, as measured in the rat tail after i.v. administration; and (f) enhancement of the rate of development of coronary collaterals in dogs equal to or better than clinically used hepain.

USE/ADVANTAGE - (I) can be used in the treatment of ischaemic heart disease such as angina and related vascular disorders and to enhance the rate of development of coronary collateral perfusion, and can be used e.g, to prevent restenosis after percutaneous transluminal angioplasty. (I) are superior to previously known heparins. (I) enhance coronary collateral formation, inhibit smooth mucle cell proliferation and maintain a low level of anti-coagulant actvity in blood contributing to an antithrombolic effect without risk of haemorrha

Dwg.0/7
FS CPI
FA AB
MC CPI: B04-C02E1; B12-F02; B12-H02
ABEQ EP 536363 B UPAB: 19970716
New heparin derivatives from bovine or porcine heparin prepared by means

of the process of claims 2, 3 or 4 characterised by: having a molecular weight equal to or larger than the standard heparin, which is 9,000 for standard bovine heparin and 12,000 for standard porcine heparin, showing a sulphur content which is equal to or higher than that of the starting heparin or at least 13% w/w, having an anticoagulant activity in the anti-FXa assay of less than 10% of the standard heparin it was made from showing a ratio of APTT activity over anti-FXa activity of 3-35 showing a reduced, by at least 75%, prolongation of bleeding time compared to the standard heparin it was made from as measured in the rat tail after i.v. administration, showing enhancement of the rate of development of coronary collaterals in dogs equal to or better than clinically used heparin. Dwg.0/7

L147 ANSWER 3 OF 4 WPIX (C) 2003 THOMSON DERWENT
AN 1987-308455 [44] WPIX
CR 1987-308456 [44]
DNC C1987-131349
TI Continuous prodn. of low-mol. wt. heparin - by controlled de-polymerisation with heparinase.
DC A96 B04 D16
IN NIELSEN, J I
PA (NOVO) NOVO IND AS; (NOVO) NOVO-NORDISK AS
CYC 21
PI EP 244235 A 19871104 (198744)* EN 26p <--
R: AT BE CH DE FR GB GR IT LI LU NL SE
AU 8772253 A 19871105 (198751)
NO 8701784 A 19871123 (198801)
JP 62283102 A 19871209 (198804)
DK 8702170 A 19871031 (198806)
FI 8701909 A 19871031 (198806)
EP 244235 B1 19930120 (199303) EN 15p C08B037-10 <--
R: AT BE CH DE ES FR GB GR IT LI LU NL SE
DE 3783644 G 19930304 (199310) C08B037-10
JP 05042918 B 19930630 (199329) 10p C12P019-26
FI 89943 B 19930831 (199339) C12P019-04
ES 2052559 T3 19940716 (199430) C08B037-10
CA 1334080 C 19950124 (199511) C12P019-26
ADT EP 244235 A EP 1987-303835 19870429; JP 62283102 A JP 1987-104845 19870430; EP 244235 B1 EP 1987-303835 19870429; DE 3783644 G DE 1987-3783644 19870429, EP 1987-303835 19870429; JP 05042918 B JP 1987-104845 19870430; FI 89943 B FI 1987-1909 19870429; ES 2052559 T3 EP 1987-303835 19870429; CA 1334080 C CA 1987-536095 19870430
FDT DE 3783644 G Based on EP 244235; JP 05042918 B Based on JP 62283102; FI 89943 B Previous Publ. FI 8701909; ES 2052559 T3 Based on EP 244235
PRAI DK 1986-1968 19860430; DK 1987-2170 19870429
REP 1.Jnl.Ref; A3...8835; EP 113040; No-SR.Pub; US 4351938; US 4396762; WO 8103276
IC ICM C08B037-10; C12P019-04; C12P019-26
ICS C12M001-34
AB EP 244235 A UPAB: 19940921
Prodn. of low-molecular-wt. heparin (LMWH) is effected by (a) continuously feeding an aq. heparin soln. into a heparinase-contg. reactor to depolymerise the heparin, (b) withdrawing depolymerised heparin soln. from the reactor and subjecting it to ultrafiltration, (c) recycling at least part of the retentate to the reactor, and (d) recovering LMWH from the filtrate. The av. molecular wt. and polydispersity (Mw/Mn) of the filtrate are measured continuously or frequently, and any deviation from the desired values are counteracted by correcting depolymerisation process parameter.

USE/ADVANTAGE - The process is esp. useful for prodn. of LMWH fractions with high Xa-inhibitory and antithrombin activity (molecular wt. 4000-6000), useful as antithrombotic agents. LMWH with a narrow molecular wt. distribution is obtained without loss of yield or waste of starting

material.
Dwg.0/3
Dwg.0/3
FS CPI
FA AB; DCN
MC CPI: A03-C01; A10-E05C; A10-G01A; A12-V01; B04-C02E1; B12-H02; D05-A02D; D05-C08
ABEQ EP 244235 B UPAB: 19930922
A process for the production of low molecular weight heparin (LMW-heparin) by enzymatic de-polymerisation of heparin comprising the steps of: continuously feeding an aqueous solution of heparin into a heparinase containing reactor and therein subjecting the heparin to enzymatic depolymerisation; removing depolymerised heparin solution from the reactor, then subjecting the solution of depolymerised heparin to ultrafiltration thereby producing a retentate and a filtrate; recycling at least a portion of the retentate to the reactor, and; recovering an LMW-heparin product from the filtrate; wherein the average molecular weight and the polydispersity of the filtrate are continuously or frequently determined whereupon possible deviations from the desired values are counteracted by correcting process parameters of the enzymatic depolymerisation reaction.
0/3
ABEQ JP 93042918 B UPAB: 19931116
Prodn. of low-mol. wt. heparin (LMWH) is effected by (a) continuously feeding an aq. heparin soln. into a heparinase-contg. reactor to depolymerise the heparin, (b) withdrawing depolymerised heparin son. from the reactor and subjecting it to ultrafiltration, (c) recycling at least part of the retentate to the reactor, and (d) recovering LMWH from the filtrate. The average molecular wt. and polydispersity (Mw/Mn) of the filtrate are measured continuously or frequently, and any deviation from the desired values are counteracted by correcting depolymerisation process parameter.
USE/ADVANTAGE - The process is esp. useful for prodn. of LMWH fractions with high Xa-inhibitory and antithrombin activity (mol. wt. 4000-6000), useful as antithrombotic agents. LMWH with a narrow mol. wt. distribution is obtd. without loss of yield or waste of starting material.
(J62283102-A)

L147 ANSWER 4 OF 4 WPIX (C) 2003 THOMSON DERWENT
AN 1984-049439 [08] WPIX
DNC C1984-020861
TI Low mol. wt. heparin(s) prodn. - by depolymerising normal heparin, having improved therapeutic properties.
DC B04
IN AMAYA, E; FUSSI, F; SMITH, M R
PA (PHAA) PHARMACIA & UPJOHN; (HEPA-N) HEPAR INDS INC
CYC 18
PI ZA 8209463 A 19830822 (198408)* 10p
EP 101141 A 19840222 (198409) EN <--
R: AT BE CH DE FR GB IT LI LU NL SE
PT 76111 A 19840131 (198410)
AU 8310331 A 19840126 (198411)
JP 59020302 A 19840202 (198411)
DK 8303255 A 19840312 (198417)
ES 8402319 A 19840416 (198423)
CA 1195322 A 19851015 (198546)
JP 04042401 B 19920713 (199232) 3p C08B037-10
DK 172798 B 19990719 (199935) C08B037-10
ADT ZA 8209463 A ZA 1982-9463 19821223; EP 101141 A EP 1983-300155 19830112; JP 59020302 A JP 1983-3271 19830112; JP 04042401 B JP 1983-3271 19830112; DK 172798 B DK 1983-3255 19830714
FDT JP 04042401 B Based on JP 59020302; DK 172798 B Previous Publ. DK 8303255
PRAI US 1982-399217 19820719

REP A3...8521; GB 1157754; GB 2068011; No-SR.Pub; US 3179566; WO 8001383
IC ICM C08B037-10
ICS A61K031-73
ICA A61K031-725
AB ZA 8209463 A UPAB: 19930925
Low molecular wt. heparin fractions are prepd. by acidifying normal heparin to obtain heparinic acid of pH about 3-5, and then depolymerising this by heating in the presence of an oxidising agent to obtain a prod. of MW about 4,000-12,000 Dalton.
The prod. has a ratio of anti-thrombotic activity to anti-coagulant activity which is superior to that of normal heparin. Fractions with differing ratio's may be chosen for differing therapeutic and pharmacological purposes. Yields are better than those of 65% obtd. in a known process, and prodts. are purer (Provisional basic previously advised in Week 8402)
0/0
FS CPI
FA AB
MC CPI: B04-C02; B12-H02

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 14:31:46 ON 28 JAN 2003

FILE COVERS 1907 - 28 Jan 2003 VOL 138 ISS 5
FILE LAST UPDATED: 27 Jan 2003 (20030127/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L148 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2003 ACS
AN 1980:159298 HCAPLUS
DN 92:159298
TI Periodate oxidation and alkaline degradation of heparin-related glycans
AU Fransson, Lars Aake; Malmstroem, Anders; Sjoeberg, Ingrid; Huckerby, Thomas N.
CS Dep. Physiol. Chem. 2, Univ. Lund, Lund, S-220 07, Swed.
SO **Carbohydrate Research (1980), 80**(1), **131-45**
CODEN: CRBRAT; ISSN: 0008-6215
DT Journal
LA English
CC 6-4 (General Biochemistry)
AB Heparin, heparan sulfate, and various derivs. thereof were oxidized with periodate at pH 3.0 and 4.degree. and at pH 7.0 and 37.degree.. Whereas oxidn. under the latter conditions destroyed all of the nonsulfated uronic

acids, treatment with periodate at low pH and temp. caused selective oxidn. of uronic acid residues. The reactivity of uronic acid residues depended on the nature of neighboring 2-amino-2-deoxyglucose residues. D-Glucuronic acid residues were susceptible to oxidn. when flanked by N-acetylated amino sugars, but resistant when adjacent residues were either unsubstituted or N-sulfated. L-Iduronic acid residues in their natural environment (2-deoxy-2-sulfoamino-D-glucose) were resistant to oxidn., whereas removal of N-sulfate groups rendered a portion of these residues periodate-sensitive. Oxidized uronic acid residues in heparin-related glycans were cleaved by alkali, producing a series of oligosaccharide fragments. Thus, periodate oxidn.-alk. elimination provides an addnl. method for the controlled degrdn. of heparin.

ST heparin deriv oxidn alk degrdn

IT Oxidation
(of heparin-related glycans)

IT Uronic acids
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidn. of, in heparin-related glycans, mol. environment effect on)

IT Mucopolysaccharides, reactions
RL: PRP (Properties)
(glycosaminoglycans, periodate oxidn. and alk. degrdn. of)

IT 2073-35-0 6556-12-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(oxidn. of, in heparin-related glycans, mol. environment effect on)

IT 9005-49-6, reactions 9050-30-0 9050-30-0D, oligosaccharide derivs. 50979-27-6
RL: PRP (Properties)
(periodate oxidn. and alk. degrdn. of)

=> d his

(FILE 'HOME' ENTERED AT 11:01:05 ON 28 JAN 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 11:01:11 ON 28 JAN 2003
L1 2 S 9005-49-6 OR 9041-08-1
L2 711 S HEPARIN
L3 709 S L2 NOT L1

FILE 'HCAPLUS' ENTERED AT 11:02:06 ON 28 JAN 2003
L4 20424 S L1
L5 46986 S L3
L6 40517 S HEPARIN
E HEPARIN
L7 40527 S E3-E10
L8 228 S E14-E24
L9 100 S E25-E41
L10 851 S E58
L11 2 S E60
L12 652 S E61,E62,E63
L13 1 S E72
L14 1390 S E79
L15 80278 S L4-L14
L16 3 S L15 AND MMWH
L17 1074 S (MEDIUM OR MED)()(MOL OR MOLECULAR)()(WEIGHT OR WT OR WH)
L18 22 S (MEDIUM OR MED)()(MOL OR MOLECULAR)()MASS
L19 4 S (MEDIUM OR MED)() ATOMIC MASS
L20 10 S L15 AND L17-L19
L21 5 S L16,L20 AND L4
L22 6 S L20 NOT L21
L23 1 S L22 AND HEPARIN/TI
L24 6 S L21,L23

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L25          265 S MIDDLE()(MOL OR MOLECULAR)()(WEIGHT OR WT OR WH)
L26           27 S MIDDLE()(MOL OR MOLECULAR)()MASS
L27            2 S MIDDLE()ATOMIC MASS
L28            0 S MIDDLE()ATOMIC SIZE
L29            4 S MIDDLE()(MOL OR MOLECULAR)()SIZE
L30            3 S L25-L29 AND L15
L31            1 S L30 AND L4
L32            7 S L24,L31
L33            2 S L30 NOT L32
L34            1 S L17-L19,L25-L29 AND HEPARINASE
L35            7 S L32,L34
L36        80459 S L15 OR HEPARINASE
L37         3624 S L36 AND (KDA OR ?DALTON? OR DA)
L38           97 S L37 AND (6000 OR 6500 OR 7000 OR 7500 OR 7800 OR 8000 OR 8500
L39          417 S L37 AND (6 OR 6 5 OR 7 OR 7 5 OR 78 OR 8 OR 8 5 OR 9 OR 9 5 O
L40           51 S L37 AND (6 000 OR 6 500 OR 7 000 OR 7 500 OR 7 8 OR 7 800 OR
L41           55 S L37 AND (6 000 OR 6 500 OR 7 000 OR 7 500 OR 7 8 OR 7 800 OR
L42          823 S L37 AND (6 OR 6 5 OR 7 OR 7 5 OR 7 8 OR 8 OR 8 5 OR 9 OR 9 5
L43          428 S L38-L42 AND (MOL OR MOLECULAR)()(WEIGHT OR WT)
L44           25 S L38-L42 AND MW
L45          144 S L4 AND L43,L44
L46           99 S L45 NOT L4 (L) LOW
L47           31 S L46 AND LOW()(MOL OR MOLECULAR)
L48           68 S L46 NOT L47
L49           33 S L48 AND HEPAR?/TI
                 SEL DN AN 9 10 22 24 28 29 30 31 33
L50            9 S L49 AND E1-E27
L51           16 S L35,L50
                 E WEITZ J/AU
L52          131 S E3,E4,E7-E11
                 E HIRSH J/AU
L53          321 S E3-E7
L54          150 S L36 AND L52,L53
L55           74 S L54 AND (MW OR MMW OR MWH OR MMWH OR (MOL OR MOLECULAR)(L)(WT
L56            1 S L51 AND L55
L57           16 S L51,L56
L58           73 S L55 NOT L57
L59            1 S L58 AND 6 025 DA
L60           17 S L57,L59
L61           17 S L60 AND L4-L60
L62            7 S L61 AND (MMW OR MMWH OR MEDIUM OR MIDDLE)
L63           17 S L61 AND (KDA OR DA OR ?DALTON? OR (MOL OR MOLECULAR OR ATOM?)
L64           17 S L62,L63
                 SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 13:28:41 ON 28 JAN 2003
L65            5 S E1-E5
L66            2 S L65 AND L1

     FILE 'HCAPLUS' ENTERED AT 13:29:07 ON 28 JAN 2003
                 SET SMARTSELECT ON
L67          SEL L54 1- RN :      96 TERMS
                 SET SMARTSELECT OFF

     FILE 'REGISTRY' ENTERED AT 13:29:11 ON 28 JAN 2003
L68           95 S L67
L69            2 S L68 AND L1
L70            4 S L68 AND L3
L71            6 S L69,L70
L72           44 S L68 AND UNSPECIFIED
L73           51 S L68 NOT L69-L72
L74            1 S L73 AND OC5/ES
L75            1 S 104993-28-4/CRN
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     FILE 'HCAPLUS' ENTERED AT 13:39:27 ON 28 JAN 2003
L76           94 S L74 OR L75
L77           82 S ARIXTRA OR XANTIDAR OR FONDAPARINUX OR FONDAPARINUX(A)(NA OR
L78          111 S L76,L77
L79           93 S L78 AND L36
L80            0 S L78 AND (L17-L19,L25-L29 OR MMW OR MMWH)
L81           34 S L78 AND (MOL OR MOLECULAR OR ATOM?)()(WT OR WEIGHT OR MASS OR
L82            0 S L64 AND L78
L83            3 S L78 AND L52,L53
L84            8 S L64 AND (FIBRIN OR THROMBIN OR ANTITHROMBIN OR ANTI THROMBIN

     FILE 'REGISTRY' ENTERED AT 13:48:47 ON 28 JAN 2003
L85            2 S 9002-04-4 OR 9002-05-5
L86            1 S ANTITHROMBIN/CN

     FILE 'HCAPLUS' ENTERED AT 13:49:46 ON 28 JAN 2003
L87            5 S L85,L86 AND L64
L88           17 S L64,L84,L87
L89           11 S L88 AND ?THROMB?
L90            1 S L88 AND ?EMBOL?
L91            1 S L88 AND (?ATHEROSCLER? OR ?ARTER?)
L92            2 S L88 AND (?VENOU? OR ?VEIN?)
L93            3 S L88 AND (HEART OR ?CARDIO? OR ?CARDIA?)
                 E CARDIOVASCULAR/CT
L94        16164 S E12-E14
                 E E12+ALL
L95       307704 S E3+NT
L96        51033 S E27 OR E28+NT
                 E CORONARY ARTERY/CT
                 E E5+ALL
L97         6983 S E2
                 E CORONARY ARTERY/CT
                 E E3+ALL
L98        12923 S E2
                 E EMBOLISM/CT
L99         2166 S E3-E8
                 E E5+ALL
L100         442 S E2
L101           2 S L94-L100 AND L88
                 E BLOOD COAGULATION/CT
L102           4 S L88 AND E3-E15
                 E E3+ALL
L103           4 S L88 AND E6+NT
L104           8 S L88 AND (E14+NT OR E16+NT OR E17+NT OR E18+NT OR E20+NT OR E2
L105          17 S L88-L93,L101-L104
                 E ANTICOAGULA/CT
L106           7 S (E11+NT OR E13) AND L105
                 E E13+ALL
                 E E2+ALL
L107          17 S L105,L106

     FILE 'MEDLINE' ENTERED AT 13:56:03 ON 28 JAN 2003
L108       36413 S L1
L109       55181 S L6
L110       55181 S L108,L109
                 E MOLECULAR WEIGHT/CT
                 E E3+ALL
L111        2320 S L110 AND E5+NT
L112          14 S L110 AND (MMWH OR MMW OR (MIDDLE OR MEDIUM OR MED)()(MOLECULA
L113          10 S L111 AND L112
L114          14 S L112,L113
                 SEL DN AN 3 6 9 11
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L115          10 S L114 NOT E1-E12
L116           9 S L115 AND (MEDIUM OR MID OR MIDDLE OR INTERMEDIATE)
L117          10 S L115,L116
L118           3 S L117 AND (A7. OR C14. OR C15. OR A15.)/CT
L119           7 S L117 AND (D12. OR D8. OR D24.)/CT
L120          10 S L117-L119

     FILE 'MEDLINE' ENTERED AT 14:04:57 ON 28 JAN 2003
L121           5 S L120 AND (KDA OR DA OR ?DALTON?)
L122          10 S L120,L121

     FILE 'HCAPLUS' ENTERED AT 14:08:11 ON 28 JAN 2003

     FILE 'MEDLINE' ENTERED AT 14:08:56 ON 28 JAN 2003

     FILE 'REGISTRY' ENTERED AT 14:09:27 ON 28 JAN 2003

     FILE 'REGISTRY' ENTERED AT 14:09:48 ON 28 JAN 2003
L123           5 S L1,L85,L86,L66
L124           2 S L65 NOT L123

     FILE 'WPIX' ENTERED AT 14:10:38 ON 28 JAN 2003
L125        4364 S HEPARIN
                 E HEPARIN/DCN
                 E E3+ALL
L126        2028 S E2 OR 1867/DRN
L127         632 S E4
L128          64 S E6
L129           1 S E8
L130        5288 S V732/M0,M1,M2,M3,M4,M5,M6
L131        2485 S (B04-C02E OR C04-C02E OR B04-C02E1 OR C04-C02E1)/MC
L132         394 S C08B037-10/IC,ICM,ICS
L133        8294 S L125-L130,L132
L134        1444 S L131 AND L133
L135        8294 S L133,L134
                 E HEPARIN
L136        4968 S E3-E61/BIX
L137        8817 S L135,L136
L138        8839 S A61K031-727/IC,ICM,ICS OR L137
L139           2 S L138 AND (MMWH OR MMW OR (MIDDLE OR MEDIUM OR MED OR INTERMED
L140         395 S L138 AND (B5094 OR B5118 OR B5107 OR B4977 OR B4740)/PLE
L141         193 S L138 AND B5094/PLE
L142          34 S L141 AND M2788/PLE
L143          24 S L142 AND HEPARIN?
L144          10 S L142 NOT L143

     FILE 'WPIX' ENTERED AT 14:27:19 ON 28 JAN 2003

     FILE 'DPCI' ENTERED AT 14:27:39 ON 28 JAN 2003
                 E WO2001051525/PN
                 E EP1252194/PN
                 E WO2001002443/PN
L145           1 S E3

     FILE 'WPIX' ENTERED AT 14:28:57 ON 28 JAN 2003

     FILE 'DPCI' ENTERED AT 14:29:05 ON 28 JAN 2003

     FILE 'WPIX' ENTERED AT 14:29:42 ON 28 JAN 2003
L146           4 S (EP101141 OR EP244235 OR WO9218545 OR WO9855515)/PN
L147           4 S L146 NOT L139

     FILE 'HCAPLUS' ENTERED AT 14:31:23 ON 28 JAN 2003
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L148 1 S CARBOHYDRATE RES?/JT AND 1980/PY AND (80 AND 131)/SO

FILE 'HCAPLUS' ENTERED AT 14:31:46 ON 28 JAN 2003